Cost-effectiveness of dinutuximab beta (Qarziba®)

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, Qarziba® should be combined with interleukin-2 (IL-2).

The NCPE has issued a recommendation regarding the cost-effectiveness of dinutuximab beta (Qarziba®). Following assessment of the applicant's submission, the NCPE recommends that dinutuximab beta (Qarziba®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (EUSA Pharma) economic dossier on the cost effectiveness of dinutuximab beta (Qarziba®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **October 2018**

Summary

In May 2017, the EMA granted marketing authorisation (under exceptional circumstances) for dinutuximab beta for use in the treatment of high risk neuroblastoma, as well as in patients with relapsed / refractory (R/R) neuroblastoma. In July 2018, EUSA Pharma submitted a dossier to support the comparative and cost-effectiveness of dinutuximab beta for the treatment of high risk neuroblastoma, as well as in patients with relapsed / refractory (R/R) neuroblastoma.

Treatment with dinutuximab beta consists of 5 consecutive courses, each course comprising 35 days. The individual dose is determined based on BSA and should be a total of 100 mg/m^2 per course. Two modes of administration are possible; (1) a continuous infusion over the first 10 days of each course at a daily dose of 10 mg/m^2 or (2) five daily infusions of 20mg/m^2 administered over 8 hours on the first five days of each course. When IL-2 is combined with dinutuximab beta, it should be administered as subcutaneous injections of 6x10^6 IU/m^2/day, for 2 periods of 5 consecutive days. Dinutuximab beta is a monoclonal, chimeric antibody targeting the neuroblastoma tumour-associated carbohydrate, GD2, which is over-expressed by neuroblastoma cells. Dinutuximab beta has an orphan designation.

Retinoic acid (RA) was chosen by the applicant as the most appropriate comparator, even though in real world practice use of RA is complementary to, not an alternative for, anti-GD2 immunotherapy. This was considered broadly appropriate by the NCPE.

1. Comparative effectiveness of dinutuximab beta

The clinical evidence for the population with high-risk neuroblastoma came from APN311-302, an open-label phase 3 trial comparing dinutuximab beta plus RA (n=189) with dinutuximab beta plus RA plus interleukin-2 (n=190). The primary outcome in the trial was event-free survival at 3 years, with overall survival, overall response, incidence of relapsed or refractory disease and safety as secondary outcomes. Results from APN311-302 showed that 55.4% of people randomised to dinutuximab beta and isotretinoin without interleukin-2 had not had an event at 3 years compared with 61.2% in the group having interleukin-2 (p=0.3202).
For overall survival, 64.1% of people randomised to dinutuximab beta and RA without interleukin-2 were still alive at 3 years compared with 69.1% in the group having interleukin-2 (p=0.6114).

The clinical evidence for the R/R population (in the economic model) came from APN311-202, a prospectively designed observational study, in which 36.8% of people with relapsed disease had not had

an event at 3 years compared with 44.6% of people with refractory disease. Given the small numbers of patients in each subgroup, the observational nature of the study, and the high degree of censoring in each study, the NCPE consider that the event-free and overall survival results should be interpreted with caution.

As there was no direct evidence comparing dinutuximab beta with RA, the applicant presented a comparison of dinutuximab beta-containing regimens versus historical controls who did not receive dinutuximab beta for both the high risk and R/R populations. For the high risk population, the applicant conducted a matched adjusted indirect comparison (MAIC) analysis of APN311-302 versus a group receiving RA alone in the RCT published by Yu et al (2010). The matched-adjusted Kaplan–Meier curves for event-free and overall survival in the dinutuximab beta arm were similar to the observed trial data. For the R/R population, an unadjusted indirect comparison was made using APN311-202 versus data on relapsed patients from the historical control. Considering the quality of the study informing the analysis, together with the naive indirect nature of the comparison, the NCPE considers the results for the R/R population to be unreliable and recommends that any conclusions around comparative effectiveness made be treated with caution.

2. Safety of dinutuximab beta

Overall, the safety of dinutuximab beta was evaluated in 514 patients with high-risk and R/R neuroblastoma, who received it as a continuous infusion (n= 98) or as repeated daily infusions (n=416). It was combined with RA in most patients and with IL-2 in 281 patients; 207 patients received dinutuximab beta as monotherapy. The most common adverse reactions that were reported in clinical trials were pyrexia (88%) and pain (77%) that occurred despite analgesic treatment. Other frequent adverse reactions were hypersensitivity (63%), thrombocytopenia (62%), vomiting (57%), diarrhoea (51%), increased transaminases (53%), pruritus (49%), capillary leak syndrome (40%) and hypotension (39%).

3. **Cost effectiveness of dinutuximab beta**

The company developed a de novo model in Microsoft Excel® to assess the cost-effectiveness of dinutuximab beta given in combination with RA, in comparison with RA. A partitioned survival method was used to model treatment effectiveness, which used the event-free and overall survival data from the MAIC of dinutuximab beta and RA to determine mortality and disease progression for each cycle. In its original model the applicant used Kaplan–Meier data from APN311-302 and from ANBL0032 (as reported by Yu et al. 2010) up to 70 months and then extrapolated event-free and overall survival. However, the NCPE noted that the longer-term data from ANBL0032 (Saramango et al 2015) included up to 12 years of RA data. The NCPE considered it more appropriate to use the longer term data

(Saramango et al 2015) because this would reduce the uncertainty that arises from extrapolating data. The applicant submitted a revised analysis which used the longer-term data for the comparator arm and extrapolated event-free and overall survival. The NCPE explored a range of extrapolations of the data that enabled modelling of more complex hazard functions, allowing for the relative treatment effect to vary over time. The NCPE noted that different extrapolations of long-term survival had a large effect on the ICER, even though the actual difference in the survival rate predicted by the extrapolations was small. The NCPE recognised that the long-term benefit of dinutuximab beta was the main source of uncertainty in the appraisal.

Results

The following base case deterministic ICER results were presented as part of the applicant's analysis;

High Risk Population

Dinutuximab beta is associated with incremental costs of €170,152 and incremental QALYs of 1.53 compared with RA, resulting in an ICER of €110,864/QALY.

R/R population

Dinutuximab beta is associated with incremental costs of €188,663 and incremental QALYs of 4.3 compared with RA, resulting in an ICER of €44,308/QALY.

The NCPE has concerns with the clinical evidence used in the economic analysis and the internal validity of the model. The NCPE therefore suggested a number of changes to the model based on plausible alternative assumptions. These changes resulted in the following estimates;

High Risk Population

Dinutuximab beta is associated with incremental costs of €169,866 and incremental QALYs of 1.13 compared with RA, resulting in an ICER of €150,994/QALY.

R/R population

Dinutuximab beta is associated with incremental costs of €186,592 and incremental QALYs of 2.93 compared with RA, resulting in an ICER of €63,486/QALY.

Sensitivity analysis

The NCPE noted the uncertainty surrounding the long term clinical benefit of dinutuximab beta. Due to a number of concerns with the economic analysis, the NCPE conducted a probabilistic sensitivity analysis for the high risk population only. The probability of cost-effectiveness at willingness to pay

thresholds of €45,000 and €20,000/QALY was 11% and 0% respectively. Given the limitations of the clinical evidence, a PSA was not run for the R/R population.

4. Budget impact of dinutuximab beta

The list price of dinutuximab beta is €8,600 per vial 20mg vial and the dose is based on the patients BSA. The cost per patient per treatment course is approximately €217,598 and €237,868 for the high risk and R/R populations, respectively. The applicant estimated that 7 patients (5 high risk and 2 R/R) would start dinutuximab beta therapy each year. The five year cumulative gross drug budget impact is estimated to be in the range of €7.4m to €7.8million. Since dinutuximab beta does not result in cost offsets due to displacement of other drugs, the net budget impact is the same as the gross budget impact.

5. Patient submission.

A patient organisation submission of evidence was received from the Childhood Cancer Foundation, during the course of this appraisal, and was included in full in the final report to the HSE.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that dinutuximab beta (Qarziba®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.