Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1625 – Dinutuximab beta (Qarziba®) for high-risk neuroblastoma

Applicant: EUSA Pharma (UK) Ltd (KMC HealthCare Pty Ltd)

Date of MSAC consideration: MSAC 79th Meeting, 28-29 July 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The application requested public funding of dinutuximab beta (DB) for the treatment of high-risk neuroblastoma (HRNBL) in patients who have previously received induction chemotherapy and achieved at least a partial response.

DB was assessed as suitable for assessment by MSAC for joint funding by the Commonwealth and the States/Territories under the National Health Reform Arrangements (NHRA) on the basis that it will be predominantly administered to admitted patients in public hospitals. As part of the NHRA arrangements, State and Territory Health Departments were provided an opportunity to make submissions to MSAC on the funding proposal.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported joint Commonwealth and State/Territory funding of DB for HRNBL in patients who have previously received induction chemotherapy and achieved at least a partial response, subject to the applicant agreeing a price reduction for DB. In providing this advice, MSAC considered the best estimate of the incremental cost effectiveness ratio (ICER) of treatment was between $**redacted** and $**redacted** per quality adjusted life year gained (QALY). However, the MSAC considered a lower incremental cost per QALY to be appropriate.

Consumer summary
KMC Health Care Pty Ltd (on behalf of EUSA Pharma (UK) Ltd) applied for joint Commonwealth and State/Territory funding of dinutuximab beta (DB) for high-risk neuroblastoma in patients who have been treated with chemotherapy and achieved at least a partial positive response.

Consumer summary

Neuroblastoma is a rare type of cancer that mainly occurs in young children and has a poor long-term outlook. DB is an antibody that attacks neuroblastoma cells. The treatment is given into a vein over the first 5 or 10 days of a 35-day cycle. Patients have 5 cycles in total of DB treatment.

The applicant proposed to MSAC that adding DB to treatment using only retinoic acid (RA) would benefit patients. However, there are no clinical trials that directly compare DB+RA with RA alone. This meant the applicant had to use an indirect comparison of a clinical trial that gave DB+RA to patients with a clinical trial that compared a similar treatment to RA alone, to show whether DB works. This meant MSAC could not be as certain about the size of the clinical benefit as it would have been if there was a clinical trial that directly compared the two treatments. After considering all the evidence available, MSAC accepted that DB can be an effective treatment for high risk neuroblastoma.

Treatment with DB is expensive – both because of the price of DB itself, and because patients may need to stay in hospital for most of the days on which treatment is given. Patients may need a lot of nursing and medical support to help with one of the main side effects of DB, which is pain while it is being given. The States and Territories cover public hospital costs, including the costs of any treatments or medicines that patients receive while being treated in a public hospital. The Commonwealth pays a contribution towards these costs. Representatives of the Commonwealth and State and Territory governments have been working together to find the best way to deliver and fund care for people with high risk neuroblastoma.

MSAC noted the high need for additional effective treatments for people with neuroblastoma and agreed, on the balance of evidence, DB should be funded. However, MSAC questioned the high cost of DB put forward in the application.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported public funding for DB in patients with high-risk neuroblastoma, as long as a lower price can be negotiated. MSAC also noted that a number of other measures need to be put in place to manage the use of public funds for DB and that these measures will need to be agreed between the applicant and Commonwealth and State/Territory Governments.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the application requested public funding for DB for HRNBL as a high-cost highly specialised therapy (HST) under the NHRA.

MSAC acknowledged the high clinical need for effective treatments for HRNBL, a rare disease that predominantly occurs in young children and has a 5-year survival rate of 40–50%. Children with HRNBL can currently access dinutuximab alpha (a different product) under expanded access schemes, but continuity of supply is not guaranteed.

MSAC noted the comparator for this application is retinoic acid (RA) alone. MSAC noted that, due to the lack of direct trial evidence comparing DB plus RA with RA alone, the submission used a matched adjusted indirect comparison (MAIC) to support the claim of superiority. This led to a number of potential biases and a highly uncertain treatment effect. However, MSAC also noted an evaluation of the MAIC by the UK National Institute of

Health and Care Excellence (highlighted in the applicant's pre-MSAC response), which also acknowledged the limitations of the MAIC but noted that higher quality data were unlikely to become available.

MSAC noted the information from the applicant's hearing that DB treatment can be completed as a short-term infusion (STI) or long-term infusion (LTI). The applicant claimed the LTI is associated with fewer adverse effects. The applicant also claimed that DB treatment should be initiated as an inpatient, but that patients may be able to transition to outpatient care during the course of the initial cycle and for subsequent cycles. However, the applicant acknowledged that there is little experience with this model of care in Australia. Regarding the side effect profile, the applicant noted that most studies had used DB in combination with interleukin-2 (IL2), which has been associated with increased adverse effects and no additional survival benefit, and IL2 is no longer used as part of DB treatment. MSAC noted that patients who received DB treatment without IL2 had fewer adverse effects compared to DB with IL2, but the evidence base to support the safety of DB in an outpatient setting is very limited.

MSAC noted the information from States/Territories that dinutuximab (alpha or beta) has been used in public hospitals for the past 5 years and is considered standard care, so no major implementation issues are expected.

MSAC noted the respecified economic evaluation supported by the MSAC Evaluation Sub-Committee (ESC) resulted in an incremental cost-effectiveness ratio (ICER) of $**redacted**. Additional information on ancillary costs provided by New South Wales Health (see Table 4) resulted in an ICER of $**redacted**.

MSAC noted the applicant's pre-MSAC response maintained that the Gompertz extrapolation method should be used in the economic modelling. However, MSAC considered this was the least conservative choice and favoured the intervention. MSAC agreed with the MSAC ESC that the Weibull extrapolation method was a more conservative option and appropriately resulted in some convergence of survival curves over time.

MSAC considered the ICER was likely to be between $**redacted** and $**redacted** per quality-adjusted life year (QALY). However, MSAC noted a number of uncertainties remained, including the magnitude of the treatment effect, the cost of administering DB and the total cost of DB per patient. These uncertainties meant the ICER range may be underestimated. MSAC noted a price reduction of approximately **redacted**% to **redacted**% would result in the ICER range lying largely under $**redacted** and considered that treatment with DB would be acceptably cost-effective at this reduced price. Further, MSAC recommended a risk sharing arrangement to manage use in NBL other than HR and to ensure the average cost per patient does not exceed the amount recorded in Table 16, recalculated to reflect the lower price recommended by MSAC.

The Department informed MSAC that it would continue to work with the States/Territories on their costing methodology but noted any additional information for DB was unlikely to be particularly informative for estimating the cost-effectiveness of treatment as it is not possible to accurately cost treatment involving the comparator alone, and therefore to estimate the incremental cost of adding DB. However, accurate estimates of the cost of treatment, both drug and ancillary costs, are needed to inform the financial estimates and to allow DBs inclusion into the activity based funding (ABF) systems that underpin the NHRA.

MSAC requested the Department provide the Independent Hospital Pricing Authority with updated financial estimates incorporating the revised cost for DB and reflecting the input

from NSW on the total cost of care for patients with this condition (see Table 3). MSAC noted the States' advice that they have been using dinutuximab alpha in public hospitals for some years means the only additional costs to hospitals should be those associated with DB.

MSAC supported public funding of DB for HRNBL, subject to the applicant agreeing to a price reduction as detailed above.

MSAC considered access criteria for DB should be consistent with the TGA indication and noted use of DB outside of the access criteria (i.e., in patients with relapsed refractory NBL) could be appropriately be managed with a risk sharing arrangement.

4. Background

An application to include DB on the Pharmaceutical Benefits Scheme (PBS) was submitted for consideration at the March 2020 Pharmaceutical Benefits Advisory Committee (PBAC) meeting. During the evaluation process it was determined that DB was likely to be predominantly administered as an inpatient treatment in tertiary public hospitals. This means it may be more appropriately funded jointly by the Commonwealth and the States and Territories through the NHRA. The submission was subsequently referred to the July 2020 meeting of the MSAC, which has assessed all previous applications for funding of high-cost HST through the NHRA.

The initial application to the PBAC (made in parallel with the TGA assessment) was for HR and relapsed refractory (RR) neuroblastoma. This application is for HR disease only, consistent with the TGA indication approved in March 2020.

DB is an antibody directed against the carbohydrate moiety of disialoganglioside 2 (GD2), which is overexpressed on neuroblastoma cells. DB induces cell death through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

Dinutuximab alpha (Unituxin®) is a similar but different GD2 antibody to DB. Dinutuximab alpha (DA) is not registered in Australia. The Department of Health (Commonwealth) understands most Australian patients with this condition are currently treated with DA, accessed either through clinical trials or a compassionate access scheme, with the latter using TGA Special Access Scheme arrangements.

5. Prerequisites to implementation of any funding advice

DB was approved for registration by the TGA on 17 March 2020, for the treatment of high-risk neuroblastoma in patients who have previously received induction chemotherapy and achieved at least a partial response.

6. Proposal for public funding

The proposed eligibility criteria for treatment of HRNBL with DB, as originally proposed for the PBS are provided in Table 1.

Table 1 Eligibility criteria

Severity:	High Risk
Condition:	Neuroblastoma
PBS Indication:	For the maintenance phase of High Risk Neuroblastoma
Treatment phase:	Initial and Continuing
Treatment criteria:	Must be treated by a specialist experienced in the use of oncological therapies
Clinical criteria:	High risk neuroblastoma Patient must have an established diagnosis of neuroblastoma according to the International Neuroblastoma Staging System (INSS) AND High risk neuroblastoma, defined as either: • INSS stages 2, 3, 4 or 4s with MYCN amplification of any age regardless of patient's age at the time of diagnosis • INSS stage 4 according to INSS without MYCN amplification aged ≥12 months at diagnosis AND Patient must have responded completely or partially to myeloablative therapy and ASCT, AND Patient must have had an ASCT.
Population criteria:	Patients aged from 12 months at diagnosis.
Cautions:	Females of childbearing age need to have a negative pregnancy test and agree to use of an effective birth control method. No breast feeding is permitted.

Source: Table 1, p4 of the Departmental Overview

The proposed PBS listing included a population criterion limiting use to patients over 12 months of age at diagnosis, reflecting the draft TGA indication at the time of submission to the PBAC. However, the approved TGA indication does not restrict DB based on age.

The proposed eligibility criteria supported by MSAC are summarised in Table 2.

Table 2 Eligibility criteria supported by MSAC

Indication:	High Risk Neuroblastoma
Treatment criteria:	Patient must be treated in a tertiary public hospital with appropriate credentials AND Patient must be treated by a specialist experienced in the use of oncological therapies
Clinical criteria:	Patient must have high risk neuroblastoma AND Patients must have previously received induction chemotherapy and achieved at least a partial response

7. Summary of State and Territory feedback

Health Victoria provided a consolidated submission incorporating feedback on behalf of all States and Territories. Additionally, NSW Health provided costing data to further inform the economic model (discussed below).

The submission confirmed dinutuximab (alpha or beta) has been used in public hospitals to treat NBL for the past 5 years and no major implementation issues were anticipated.

The submission stated there were diverse opinions on whether DB would be primarily administered as an inpatient or an outpatient but acknowledged the evidence base for substantial use in the outpatient setting was weak.

NSW provided an estimate of the ancillary costs associated with the use of DB compared to the use of RA alone. NSW estimated the total average clinical cost per patient treated with (i) RA alone was $**redacted** (plus a contingency cost of $**redacted**) and (ii) DB + RA would be $**redacted** (plus a contingency cost of $**redacted**) (Table 3).

Table 3 NSW Health estimated total ancillary (administration) cost

	Total ancillary (administration) cost	Contingency cost
RA alone	$redacted	$redacted
DB + RA	$redacted	$redacted

Based on these costings, the incremental cost of administration of DB was estimated to be $**redacted**[1] (plus $**redacted** contingency cost per patient), compared to $**redacted** in the MSAC ESC report. NSW Health acknowledged there were considerable uncertainties associated with the cost estimate and noted there was likely to be a range of treatment costs depending on individual patients. MSAC noted the ICER incorporating the cost estimated by NSW was $**redacted**.

Table 4 ICER incorporating NSW Health estimated costs

	Incremental ancillary (administration) cost	ICER
MSAC ESC	$redacted	$redacted
NSW Health estimated costs (contingency)[1]	$redacted ($redacted)	$redacted

1. NSW Health, communications dated 30/6/20, 20/7/20 and 24/7/20. Contingency cost not included in economic model.

8. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from 31 individuals, two health care professionals and two organisations which described a range of benefits of treatment with DB. Comments from the health professionals also noted that treatment with DB could lead to serious and significant toxicity (e.g. pain, inflammation, inflammatory responses, fluid overload) but claimed that the majority of these could be managed in experienced paediatric oncology centres.

The applicant's pre-MSAC response provided two consultation responses from paediatric oncology consultants based in Europe who summarised their clinical experience in administering DB using the long term infusion (i.e. rate of 10mg/m^2/day continuously for 10 days) compared to the short term infusion (i.e. rate of 20mg/m^2/day over 8 hours per day for 5 days). The clinicians noted that the long term infusion regimen facilitates administration in an outpatient setting and state clinical practice in Europe has evolved to include the long term infusion regimen as the preferred DB treatment regimen.

9. Proposed intervention's place in clinical management

Description of Proposed Intervention

Treatment with DB consists of five consecutive courses, each course comprising 35 days. Two modes of administration are possible: five daily infusions administered over 8 hours, on the first 5 days of each course, herein referred to as the "short term infusion" (STI) or a continuous infusion over the first 10 days of each course, herein referred to as the "long term infusion" (LTI). The doses administered for the STI and LTI are summarised in Table 5. DB must be administered under the direction of a physician experienced in the use of oncological therapies and in an environment where full resuscitation services are immediately available.

[1] $redacted - $redacted = $redacted

Table 5 Administration of dinutuximab beta

		STI	LTI
Total dose per course:	Patients weighing > 5kg to ≤12kg Patients weighing > 12kg	3.3mg/kg 100mg/m^2	
Course description		Daily infusions over 8 hours on first 5 days of each 35 day course	Continuous infusion over first 10 days of each 35 day course
Infusion dose:	Patients weighing > 5kg to ≤12kg Patients weighing > 12kg	0.66 mg/kg 20 mg/m^2 BSA	0.33 mg/kg 10 mg/m^2 BSA

BSA body surface area; LTI long term infusion; STI short term infusion
Source: Product Information

The applicant claimed most use in clinical practice will be with the LTI due to improved tolerability. The LTI is administered as two infusion pumps per course each lasting 5 days. The clinical trial evidence for DB for HRNBL provided in support of the submission predominantly uses the STI. Evidence for the LTI for HRNBL is only available from a poster presentation to ASCO 2019 (See also Section 8 and 9).

RA is administered concomitantly with DB at a dose of 160 mg/m²/day orally over 14 days for a total of 6 cycles.

Prior to starting each treatment course, pulse oximetry, bone marrow function, liver function and renal function should be measured and treatment delayed until adequate function is demonstrated (refer to Product Information for details).

Patients should receive concomitant treatment with morphine, gabapentin and paracetamol/ ibuprofen for pain management and antihistamine to prevent hypersensitivity reactions.

Description of Medical Condition(s)

NBL is an embryonal tumour of the autonomic nervous system. It usually occurs in very young children. 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.

Current practice for the staging and risk classification of NBL is through the International Neuroblastoma Risk Group (INRG) staging system. The INRG categorises tumours as very low risk, low risk, intermediate risk or high risk (HR) 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).

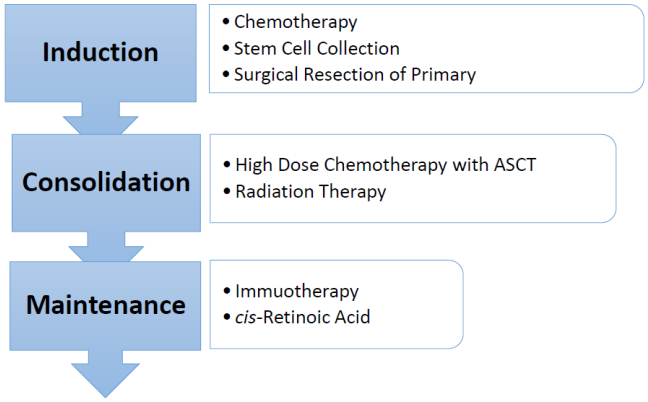
An Australian study found the average age-adjusted incidence of NBL from 1983 to 2015 was 9.5 cases per million children per year[2]. Over the duration of the study, more than half of patients were diagnosed with metastatic disease and the 5 year cause-specific survival for these patients was 49.5%. Over time, a trend to a lower proportion of patients being diagnosed with metastatic disease and a higher 5 year cause-specific survival was observed, although outcomes remained poor for patients over 18 months of age diagnosed with metastatic disease (5 year cause-specific survival 46%).

[2] Youlden D, Jones B, Cundy T et al. Incidence and outcomes of neuroblastoma in Australian children: A population-based study (1983 – 2015) [published online ahead of print, 2020 Feb 18]. J Paediatr Child Health. 2020;10.1111/jpc.14810.

Clinical management of HRNBL

The clinical management of HRNBL is summarised in Figure 1. Generally, following chemotherapy and surgical resection, patients receive an autologous stem cell transplant (ASCT) according to local treatment protocols followed by maintenance therapy with immunotherapy (DA or DB) plus retinoic acid (RA).

Figure 1 HRNBL treatment overview



ASCT autologous stem cell transplant
Source: Figure 1, Smith and Foster, 2018[3]

10. Comparator

The comparator for this application is RA alone.

11. Comparative safety

The TGA approved Product Information (PI) for DB reports that the safety of DB has been evaluated in 514 patients with HR and RR NBL with 98 patients receiving the LTI and 416 receiving the STI. Most patients received DB in combination with RA and 307 also received IL-2. The most common adverse reactions were pyrexia (88%) and pain (77%) that occurred despite analgesic treatment. Other frequent adverse reactions were hypersensitivity (63%), vomiting (57%), diarrhoea (51%), capillary leak syndrome (CLS) (40%) and hypotension (39%). The combination of DB with IL-2 increases the risk of adverse drug reactions compared to DB without IL-2, especially for pyrexia (92% vs. 79%), CLS (50% vs. 25%), pain related to DB (75% vs. 63%), hypotension (43% vs. 26%), and peripheral neuropathy (14% vs. 7%), respectively.

The applicant claimed the LTI is better tolerated than the STI; however, safety data for use of the LTI in HRNBL is from Study 302-R4, which is only provided as a conference presentation. A naïve comparison of the DB +RA treatment arms across Study 302-R2 and Study 302-R4 is inconclusive, with some grade 3/4 adverse events (AEs) appearing at lower rates, some higher and some similar (Slide 15, Ladenstein 2019b presentation). The TGA Product Information does not include any information that supports the applicant's claim of improved tolerability of the LTI.

There is limited safety data in children under 12 months of age.

[3] Smith and Foster. High-risk neuroblastoma treatment review. Children 2018; 5, 114.

The applicant's pre-MSAC response reiterated the advantages of LTI administration claiming greater tolerability of LTI versus STI with comparable efficacy demonstrated by:

- low pain scores, reduced i.v. morphine usage and low frequency of Grade ≥3 adverse events that allowed outpatient use of DB; and
- treatment-emergent adverse events (TEAE) leading to discontinuation and TEAEs associated with infusion rate (i.e. pain or allergy of grade ≥3) are reduced for LTI compared to STI administration.

12. Comparative effectiveness

There are three DB studies relevant to the application: Study 301, Study 302-R2 and Study 302-R4. Study 301 was a direct randomised study comparing DB to RA but the study was terminated before completion, after trial results for dinutuximab alpha demonstrated the superiority of immunotherapy vs RA (Yu 2010), it was deemed unethical to continue to treat patients with RA alone.

Study 302 is a clinical trial conducted by the SIOPEN[4] group, which includes five distinct within-trial randomisations (R0, R1, R2, R3 and R4) of patients with HRNBL comparing various treatments throughout the treatment pathway. The R2 and R4 randomisations of Study 302 provide the key clinical evidence for the STI and LTI dosing schedules of DB respectively for HRNBL. Results from Study 302-R2 have been published (Ladenstein 2018) but results from Study 302-R4 are only available from a presentation to ASCO 2019 (see Table 6).

In the absence of direct trial evidence (DB+RA vs RA), a matched adjusted indirect comparison (MAIC) was conducted to compare patients treated with DB in Study 302-R2 to patients treated with RA in Yu 2010 (the pivotal trial comparing dinutuximab alpha to RA).

A number of other studies and naïve comparisons were presented in the PBAC submission for DB (refer to Table 3 and Table 5 in the PBAC ESC advice). The remainder of this PSD discusses only those studies relevant to the key comparisons. Details of the relevant studies are provided in Table 6.

[4] International Society of Paediatric Oncology European Neuroblastoma Research Network

Table 6 Relevant trials, studies and associated reports

Trial ID	Protocol title/ Publication title	Publication citation
Dinutuximab beta studies		
301	APEIRON Biologics AG (2016d). APN311-301: Summary report: high risk neuroblastoma study of SIOP-Europe (SIOPEN) HR-NBL/SIOPEN - interim data analysis of safety and efficacy data from the 'unmodified' R2 randomization - Final 1.	16 March 2016
302-R2	APEIRON Biologics AG (2016b). APN311-302: Interim data analysis on safety and efficacy of ch14.18/CHO from data collected in the high risk neuroblastoma (HRNBL1) study 1.5 of SIOP-Europe (SIOPEN): Final Version 1.0.	17 March 2016
	Ladenstein R, Potschger U, Valteau-Couanet D et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial.	The Lancet. Oncology 2018. 19(12): 1617-1629.
302-R4	Ladenstein R, Potschger U, Valteau-Couanet D et al. Randomisation of dose reduced subcutaneous interleukin2 in maintenance immunotherapy with anti-GD2 antibody dinutuximab beta long-term infusion in front line high risk neuroblastoma patients: early results from the R4-HR-NBL1/SIOPEN trial.	American Society of Clinical Oncology 2019 conference presentation.
Dinutuximab alpha vs retinoic acid (source of data used for RA control arm in MAIC)		
Yu et al 2010	Yu A, Gilman A, Ozkaynak F, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma.	NEJM 2010 363(14): 1324-1334.
Dinutuximab beta vs retinoic acid MAIC		
HRNBL		
EUSA Pharma MAIC study (302-R2 vs Yu et al 2010)	EUSA Pharma (UK) ltd. Study 302-Matching Adjusted Indirect Comparison (MAIC) Analysis.	Analysis report (no date provided with submission)^.

GD2 disialoganglioside; GM-CSF granulocyte-macrophage colony-stimulating factor; HRNBL high risk neuroblastoma; MAIC matched adjusted indirect comparison

^ Results reported in NICE TA538, 22 August 2018.

Source: Table 3, p7 of Departmental Overview

The key features of the included clinical evidence are summarised in Table 7.

Table 7 Key features of the relevant evidence

Trial/study	N	Design/ duration	ROB	Intervention(s)	Outcome(s)
Study 301: terminated (SIOPEN R2 unmodified)	34	R, OL, MC, Phase III	Low[a]	DB (STI) + RA vs. RA	Primary: EFS Secondary: OS, relapsed/progressed pts, deaths
Study 302-R2 (SIOPEN R2 revised)	406	R, OL, MC, Phase III	Low	DB (STI) + RA + IL-2 vs. DB (STI) + RA	Primary: 3-yr EFS[b] Secondary: OS, cumulative incidence of relapse/progression and death
Study 302-R4 (SIOPEN R4)	408	R, OL, MC, Phase III	Low	DB (LTI) + RA vs. DB (LTI) + RA + IL-2 (50% of dose used in R2)	Primary: EFS Secondary: response, OS, toxicity
Yu et al 2010 (COG trial)	226	R, OL, MC, Phase III	Low	DA + GM-CSF + IL-2 + RA vs. RA	Primary: EFS Secondary: OS

DA dinutuximab alpha; DB dinutuximab beta; EFS event free survival; HRNBL high risk neuroblastoma; GM-CSF granulocyte-macrophage colony-stimulating factor; Il-2 interleukin 2; LTI long term infusion; MC multi centre; NR non randomised; OL open label; OS overall survival; R randomised; RA retinoic acid; STI short term infusion;

[a] The study was terminated early and therefore did not meet the pre-specified sample size.

[b] Calculated from the date of the modified R2 randomisation. Disease progression or relapse, death from any cause and second neoplasm were considered as events

Source: Study 301 CSR; p23 of Study 302-R2 CSR, Ladenstein 2019b presentation.pptx, Yu et al 2010

All the DB studies defined HRNBL using the International Neuroblastoma Staging System (INSS), rather than the INRG which is currently used in clinical practice. The key difference between the two staging systems is that the INSS uses results from surgery to stage neuroblastoma, whereas the INRG allows for pre-treatment risk stratification.

The key clinically relevant outcomes were overall survival (OS), event free survival (EFS) and safety. EFS was defined as the time from enrolment to the first occurrence of relapse, progressive disease, secondary cancer, or death. The primary efficacy outcome in Study 301, Study 302-R2, Study 302-R4 and Yu 2010 was 3-year EFS (however Study 301 was terminated and Yu 2010 was stopped early).

Study 301 recruited 35 patients before the study was terminated; therefore, the results from this study are not informative and are not presented below. The results for Study 302-R2 and Study 302-R4 are presented in Table 8.

Table 8 EFS and OS outcomes for Study 302-R2 and Study 302-R4

Trial/Study	Study 302-R2 (FAS)		Study 302-R4 (ITT)	
	DB (STI) + RA	DB (STI) + IL-2 + RA	DB (LTI) + RA	DB (LTI) + IL-2 + RA
N	180[a]	190[a]	205	203
EFS				
Events	79 (44.1%)	69 (36.5%)	61	61
1-year	72.3%	72.3%	0.76 ± 0.03	0.75 ± 0.03
2-year	63.2%	66.3%	0.67 ± 0.04	0.64 ± 0.04
3-year	redacted%	redacted%	NR	NR
4-year	redacted	redacted	NR	NR
p-value	redacted[b]		0.649	
OS				
Deaths	60 (33.5%)	56 (29.8%)	40	39
1-year	86.3%	87.9%	0.89 ± 0.02	0.89 ± 0.02
2-year	76.0%	75.4%	0.82 ± 0.03	0.78 ± 0.04
3-year	64.1%	69.1%	NR	NR
4-year	redacted	redacted	NR	NR
p-value	redacted[c]		0.655	

EFS event free survival; FAS full analysis set; IL2 interleukin 2; ITT intention to treat; LTI long term infusion; NR not reported; OS overall survival; STI short term infusion;

[a] 1 patient with missing date of death and without progression was excluded from the analysis

[b] Adjusted for previous treatment (busulfan and melphalan, carboplatin, etoposide and melphalan). Note that the p-value refers to the overall EFS analysis and not only to the 3-year analysis

[c] Adjusted for previous treatment (busulfan and melphalan, carboplatin, etoposide and melphalan).

Source: Table 5-5, p16, Table 5-6, p17, Table 5-9, p20 of Study 302 CSR addendum; Slide 17, Ladenstein 2019 ASCO presentation.

Matched adjusted indirect comparison (MAIC)

An unanchored MAIC was conducted using most patients enrolled in Study 302-R2 (both arms) and all patients randomised to RA in Yu 2010 (aggregate data only). The analysis matched patients in Study 302-R2 by estimating propensity score weights so that the mean across four risk factors (age, INSS stage, MYCN status, response to treatment before ASCT) would match the mean of the same risk factors in Yu 2010. The results from the MAIC are presented in Table 9 and Figure 2.

Table 9 Results of the MAIC, DB STI + RA ±IL2 (data from Study 302-R2) vs RA (data from Yu 2010)

Trial/Study	EUSA Pharma MAIC	
	Data from Study 302-R2	Data from Yu 2010
	DB STI +RA ±IL2	RA
N	245#	113
EFS		
Events	redacted	51
1-year	redacted	0.69
2-year	redacted	0.46
3-year	redacted	0.46
5-year	redacted	0.43
Hazard ratio	redacted (redacted, redacted)	
Survival		
Deaths	redacted	33
1-year	redacted	0.90
2-year	redacted	0.75
3-year	redacted	0.63
5-year	redacted	0.50
Hazard ratio	redacted (redacted, redacted)	

DB dinutuximab beta; EFS event free survival; IL2 interleukin 2; LTI long term infusion; NR not reported; RA retinoic acid; OS overall survival; STI short term infusion;
There was a discrepancy in patient numbers between the MAIC methodology and analysis report (n=245) and the Sponsor's submission (n=160)
Source: Table 6, p9 of the Departmental Overview

Figure 2 Kaplan Meier of EFS and OS for DB + RA ± IL2 (302-R2) vs RA (Yu et al 2010) for HRNBL - Redacted

The potential bias and limitations of the MAIC include:

- The MAIC may not have controlled for all important risk factors (known and unknown).
- The MAIC did not adjust for type of consolidation therapy, which may impact on the outcome.
- The submission presented limited detail about the estimation of the propensity score weights, however, matching to mean aggregate values for four risk factors in Yu et al 2010 ignores the distribution and covariance of the risk factors across the comparison groups.

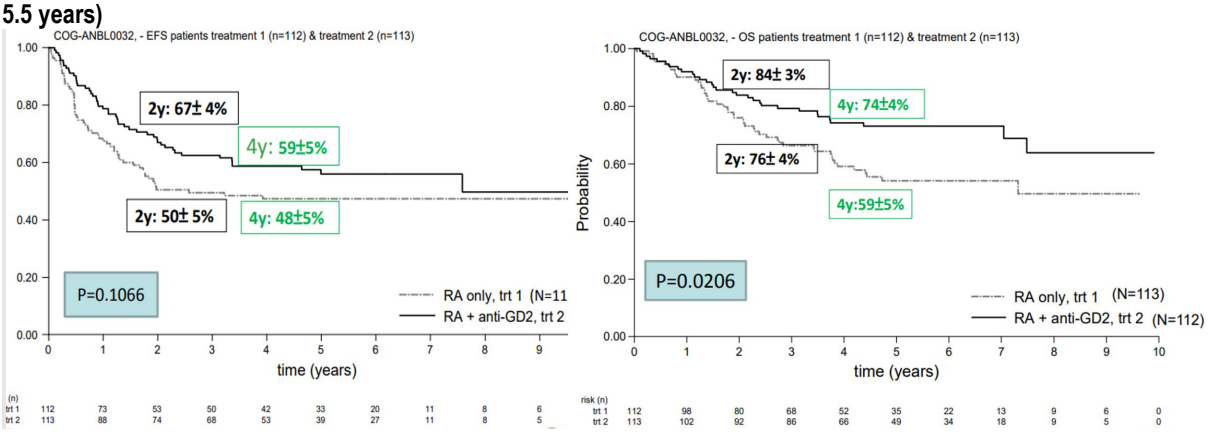
The applicant's pre-MSAC response acknowledged the potential bias and limitations of the MAIC however, the applicant claimed the validity of the outcomes have been confirmed in a reanalysis performed by NICE's Decision Support Unit (NICE Qarziba 2nd Committee Meeting slides, 10/4/2018, p.8).

Dinutuximab alpha study

Dinutuximab alpha (+ RA+ IL-2+GM-CSF) was compared to RA in the Yu 2010 study. Over 2.1 years of follow-up, the 2 year EFS was 66% vs 46% for DA and RA (p=0.01), respectively and the 2 year OS was 86% vs 75% for DA and RA (p=0.02), respectively (no hazard ratios were reported). Data from this study with longer follow-up (median 5.5 years – noting the study was unblinded prior to reaching the 3 year primary endpoint), showed the curves for EFS converged, resulting in a non-significant difference between the immunotherapy and RA monotherapy arms (Figure 3). Immunotherapy was associated with statistically significant improved survival compared to RA monotherapy, with the difference in the treatment arms for OS narrowing over time. Given that both DB and DA are anti-GD2

antibodies, it is possible that both the EFS and OS curves for DB vs RA will converge with longer follow-up.

Figure 3 EFS and OS results for dinutuximab alpha + RA + IL-2 + GM-CSF vs RA monotherapy (median follow up 5.5 years)



EFS event free survival; GM-CSF granulocyte-macrophage colony stimulating factor; IL2 interleukin 2; RA retinoic acid; OS overall survival
Source: Slide 14 and 15, Yu 2014 presentation

The PBAC ESC considered the estimated treatment effect for DB (+ RA ± IL-2) versus retinoic acid (RA) monotherapy is highly uncertain. The updated submission continued to rely on a number of adjusted and naïve indirect comparisons to support the claim of superiority of DB + RA versus RA monotherapy.

13. Economic evaluation

Three different versions of the economic model were utilised during the evaluation of this submission. All had the same structure, but differed in key components (see Table 11).

The economic model provided in the updated submission (MSAC ESC model) had the same model structure as the model in the initial submission to the PBAC: two-part (short term + long-term model) partitioned survival analysis model with three health states: stable disease (EFS; no events), failure state (FS; progressive disease) and death. The key components of the economic evaluation are summarised in Table 10.

Table 10 Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis, cost-utility analysis
Outcomes	LYs and QALYs gained
Treatments	DB + RA vs RA monotherapy for a maximum of five cycles
Time horizon	90 years in the model base case, consisting of: - a short term model (10 year "cure threshold"); and - a long term model to 90 years.
Methods used to generate results	Partitioned survival model
Health states	Stable disease (EFS), failure state (FS; progressive disease) and death
Cycle length	Monthly for the short term model; Annually for the long term model.
Transition probabilities	Transitions in the short term model are based on KM data (MAIC: 302-R2 v Yu et al) and extrapolated functions when KM data is not available. Transitions in the long term model are informed by Australian life tables, Laverdière et al 2009 and an assumption.
HRQoL	The submission first estimated paediatric population norms based on EQ-5D-5L adult population norms reported in the literature (McCaffrey et al 2016). Then a utility decrement was applied for the stable disease state (- 7.3%) and failure state (- 41.7%) based on HUI2 and HUI3 values from Portwine et al 2016 and Barr et al 1999.
Costs	The submission estimated costs for treatment, administration, concomitant medications, monitoring, management of adverse events, ongoing health state costs and cost of death.
Software package	Excel 2010

EFS event free survival; HRQoL health-related quality of life; LY life years; KM Kaplain Meier; MAIC matched adjusted indirect comparison; QALY quality adjusted life year
Source: Table 7, p11 of the Departmental Overview

The short term model accounted for the submission's proposed "cure threshold", whereby patients who do not experience disease progression or relapse by ten years are assumed "cured". All patients commence the short term model in the stable state, and are at risk of disease progression or death each cycle. Patients in the failure state remain at risk of death and cannot transition back to the stable state.

In the long term model (once the "cure threshold" is reached at ten years), patients remain in the same health state or transition to dead each cycle.

The model extrapolated OS and EFS in the DB arm after the last patient observation by using the estimated parametric regression directly, irrespective of survival at that point. The model extrapolated OS in the RA arm of the model based on the extrapolated survival in the DB arm of the model. That is, the difference between the two arms remained constant from six to ten years.

To inform transitions in the short term model, the submission used results from the MAIC analysis presented Table 9.

A summary of differences between the economic model submitted to PBAC and the economic models presented to MSAC ESC and MSAC are provided in Table 11.

Table 11 Differences between the economic model submitted to the PBAC and the models presented to MSAC ESC and MSAC

Parameter	Model considered by PBAC ESC	Model presented to MSAC ESC	Model considered by MSAC	Comment
Inpatient use	10.4 days over 50 days of treatment	19 days over 50 days of treatment	100%	The PBAC ESC requested the base case model assume all patients are treated as inpatients for the duration of their treatment (paragraph 6.50, PBAC ESC advice). This was provided as a sensitivity analysis in the updated submission.
Cost of administration	$redacted per day Based on AR-DRG R63Z	$redacted per day Based on weighting and disaggregation of a number of AR-DRGs	Based on (1) AR-DRG 165A and (2) input from NSW Health.	The PBAC ESC considered use of the AR-DRG for chemotherapy administration (R63Z) was not appropriate for dinutuximab beta (paragraph 6.45, PBAC ESC advice). The revised model used alternative AR-DRGs but the methodology applied is not appropriate (discussed further below).
Completion	Cycle 1: 100% Cycle 2: 98.1% Cycle 3: 95.9% Cycle 4: 92.1% Cycle 5: 90.2%	100% for all cycles	100% for all cycles	The PBAC ESC completion rate is tested in sensitivity analysis.
IL-2 use	11%	0%	0%	Removal of concomitant IL-2 is appropriate and consistent with approved PI.
Extrapolation method	Gompertz for DB EFS and OS	Gompertz for DB EFS and OS	Weibull	The PBAC ESC considered the Gompertz extrapolated function was the least conservative option and favoured dinutuximab beta (paragraph 6.40, PBAC ESC advice).The PBAC ESC considered convergence of the EFS and OS curves would be appropriate, noting the Yu 2014 data converged (paragraph 6.20, PBAC ESC advice). The PBAC ESC noted applying the more conservative Weibull extrapolation also resulted in some convergence of EFS and OS curves which may be more appropriate (paragraph 6.49, PBAC ESC advice). Application of a Weibull extrapolation is provided as a sensitivity analysis.
Convergence	None	None	Some (as a result of using Weibull extrapolation)	
BSA	0.63m^2	0.63m^2	0.63m^2	This value is based on the average in Study 302-R2. The PBAC ESC noted the model was sensitive to this assumption and the age and BSA of Australian patients is unknown (paragraph 6.43, PBAC ESC advice).

AR-DRG Australian Refined Diagnosis Related Groups; DB dinutuximab beta; BSA body surface area; ESC economic subcommittee; EFS event free survival; OS overall survival; PBAC Pharmaceutical Benefits Advisory Committee; PI product information
Source: Table 8, p 12 of the Departmental Overview

The result of the economic evaluation in the submission is presented in Table 12. On the basis of the advice of the MSAC ESC a revised economic model was considered by MSAC.

Table 12 Results of the economic evaluation

Component	DB	RA	Increment
Costs	$redacted	$redacted	$redacted
Life years	39.5499	29.4986	10.0513
QALYs	11.1990	8.5639	2.6351
Incremental cost/extra life year gained			$redacted
Incremental cost/extra QALY gained			$redacted

Source: Table 9, p12 of the Departmental Overview

A summary of the disaggregated costs from the model in the submission is provided in Table 13.

Table 13 Health care resource items: disaggregated summary of cost impacts

Resource item	DB cost	RA cost	Incremental cost
Treatment costs	$redacted	$redacted	$redacted
DB	$redacted	$redacted	$redacted
Administration & hospitalisation	$redacted	$redacted	$redacted
Retinoic acid	$redacted	$redacted	$redacted
Concomitant medication	$redacted	$redacted	$redacted
Management of adverse events	$redacted	$redacted	$redacted
Monitoring	$redacted	$redacted	$redacted
Stable health state	$redacted	$redacted	$redacted
Failure health state	$redacted	$redacted	$redacted
Dead health state (end of life costs)	$redacted	$redacted	$redacted
Total costs	$redacted	$redacted	$redacted

Source: Table 10, p13 of the Departmental Overview

Cost of administration

The economic model submitted to the PBAC applied the chemotherapy administration AR-DRG (R63Z) which the ESC considered was not appropriate. The revised model used more appropriate AR-DRGs but applied an inappropriate methodology to determine the cost of administration of DB.

National Hospital Cost Data Collection (NHCDC) costs should have been applied (rather than the National Efficient Price Determination costs that were applied) and the 'total cost' column for the relevant AR-DRG should be the basis for determining the unit cost for an episode of hospitalisation[5].

The applicant considered AR-DRGs I65A, I65B, K64A, Q60A and R62A were relevant to neuroblastoma hospital admissions (Table 14). The LTI of DB is given over 10 days; therefore, the average length of stay for I65A appears reasonable (9.4 days) and is tested as a per cycle cost in a sensitivity analysis. It should be noted that the cost of monitoring, concomitant medications and adverse event management are assumed to be included in the AR-DRG episode cost, rather than costed separately.

Table 14 Relevant AR-DRGs associated with administration of DB

AR-DRG	Description	No. of separations	ALOS	Cost
I65A	MUSCULOSK MALIG NEOPLASM, MAJC	1,571	9.4	$17,555
I65B	MUSCULOSK MALIG NEOPLASM, MINC	3,212	3.6	$7,454
K64A	ENDOCRINE DISORDERS, MAJC	4,305	4.0	$8,395
Q60A	RETICLENDO&IMMUNITY DIS, MAJC	10,980	4.7	$9,962
R62A	OTHER NEOPLASTIC DIS, MAJC	751	8.8	$15,920

ALOS average length of stay; AR-DRG Australian refined diagnosis related group
Source: COST WEIGHTS FOR AR-DRG VERSION 9.0, Round 21 (2016-17).

[5] http://www.pbs.gov.au/industry/useful-resources/manual/manual-of-resource-items-and-associated-unit-costs-dec-2016.pdf

Reduced hospitalisation associated with LTI

The base case economic model in the submission to MSAC ESC assumed all patients were hospitalised for the 10 days of Cycle 1, 6 days of Cycle 2, 3 days of Cycle 3 and all treatment is administered as an outpatient for Cycles 4 and 5. The applicant claimed that treatment with the LTI of DB will allow patients to be discharged from hospital early (for Cycles 2 and 3) or treated as outpatients (for Cycles 4 and 5). However, there is limited evidence available for this assumption in the HRNBL setting. Given the age and health status of patients, the adverse event profile and the requirement for significant pain management, it is likely a majority of patients will require hospitalisation for treatment. The applicant stated most European patients are treated as a combination of inpatients and outpatients for cycles 1 to 3 and exclusively as outpatients for cycles 4 and 5 but the relevance to the Australian hospital setting is unclear.

A letter from the Australian and New Zealand Childrens Haematology/Oncology Group (ANZCHOG) in support of DB makes reference to blinatumomab as an example of where the model of initiating treatment as an inpatient and then moving to outpatient treatment has provided significant benefit to patients. The Department noted, unlike the DB PI, the blinatumomab PI recommends a minimum period of hospitalisation per cycle, is administered as a continuous infusion over 28 days and does not require concomitant morphine. The difference in administration profiles of blinatumomab and DB may make the comparison unreasonable.

Discount rate

The base case economic model applied a discount rate of 5% to costs and outcomes. The applicant requested MSAC to consider applying a lower discount rate to reflect that "the incremental life gained by a young person should be valued more highly than that gained by older patients". A sensitivity analysis applying a 2% discount rate to costs and outcomes is presented below.

Using alternate data source for RA data

The submission provided a sensitivity analysis using an alternative data source for the comparator arm (RA). The analysis used data from Study 302-R1 which was a study comparing different chemotherapy regimens as consolidation therapy for HRNBL, followed by RA (refer to the PBAC ESC advice, Tables 2 to 6 for more details of this study). This analysis is a naïve comparison of single treatment arms (rather than a matched or adjusted comparison).

Sensitivity analyses

Sensitivity analyses conducted by the applicant are presented in Table 15. The MSAC consider two of these sensitivity analyses (indicated by italicised text) to be the more appropriate base-cases for decision making.

Table 15 Sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	Incremental cost per QALY
Base case	$redacted	2.6351	$redacted
Weibull extrapolation for EFS and OS for DB arm (base case Gompertz); RA arm unchanged from base case	$redacted	redacted	$redacted
100% inpatient treatment (cost $redacted per cycle)	$redacted	2.6351	$redacted
2% discount rate	$redacted	redacted	$redacted
Using data from Study 302-R1 to inform the RA treatment arm	$redacted	redacted	$redacted
100% inpatient treatment and assuming AR-DRG I65A per cycle and removing cost of monitoring, AEs and concomitant medications	$redacted	2.6351	$redacted
100% inpatient treatment and assuming AR-DRG I65A per cycle and removing cost of monitoring, AEs and concomitant medications and Weibull extrapolation	*$redacted*	*redacted*	*$redacted*
100% inpatient treatment and assuming administration cost as provided by NSW and Weibull extrapolation	*$redacted*	*redacted*	*$redacted*

AE adverse event; DB dinutuximab beta; EFS event free survival; RA retinoic acid; OS overall survival
Source: ModelHR, Cell GR: GV: $redacted AND Results, W13, W14 and W15 = $0 [and Results D11, F11 to Weibull]

Cost per patient

The total drug and administration cost per patient (based on a BSA of 0.63m^2), is summarised in Table 16.

Table 16 Cost per patient

	DB cost	Administration cost	Total
Base case (assuming 38% of inpatient treatment i.e. 19 days out of 50 days)	$redacted	$redacted	$redacted[1]
Base case (assuming 100% of inpatient treatment)	$redacted	$redacted[2]	$redacted
Sensitivity analysis assuming 100% inpatient treatment and AR-DRGI65A	$redacted	$redacted[3]	$redacted
100% inpatient treatment and administration costs as estimated by NSW	$redacted	$redacted	$redacted

1. Does not include cost of concomitant medication ($redacted), management of AEs ($redacted) and cost of monitoring ($redacted)
2. $redacted for 5 cycles
3. $redacted for 5 cycles
Source: Table 13, p17 of the Departmental Overview

The applicant's pre-MSAC response presented a number of revised ICERs that explored (i) a reduction in hospital stay from 10 to 5 days to reflect STI protocol (ii) alternate AR-DRG codes (iii) alternate parametric extrapolation methods and (iv) variable discount rates.

14. Financial/budgetary impacts

The applicant's estimated overall cost of providing public funding for DB is summarised in Table 17. This estimate assumes 19 days of inpatient treatment (out of 50 days) consistent with the assumption applied in the base case economic model. The MSAC considered the estimated number of patients with HRNBL was reasonable and noted the total drug cost will need to be updated following agreement on a revised price.

Table 17 Financial impact

	Assumption	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients							
With NBL	Incidence of 10.4 per million 0 to 14 year olds	50	52	54	55	57	59
With HRNBL	~56%	28	29	30	31	32	33
Drug cost							
Total vials	redacted per cycle (based on BSA of 0.63m^2) for 5 cycles	redacted	redacted	redacted	redacted	redacted	redacted
Total drug cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Administration costs							
Hospital admission costs[1]	Assuming 19 days inpatient treatment[2]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost		$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

1. Summary worksheet, D43 to I43
2. Inpatient cost $redacted plus cost of monitoring, concomitant medications and AEs

Source: Table 14, p15 of the Departmental Overview

The applicant presented a sensitivity analysis assuming patients used 5 vials of DB per cycle which increased the drug cost to $**redacted** in Year 6.

Assuming the cost of administering DB is $**redacted** per cycle per patient (including the cost of monitoring, concomitant medications and AEs), the total hospital admission cost would be $**redacted** in Year 1, increasing to $**redacted** in Year 6.

The estimated overall financial cost of public funding for DB and assuming 100% inpatient treatment using AR-DRG I65A is provided in Table 18. It should be noted that the hospital cost is likely being incurred currently with the use of DA (under the compassionate access program). MSAC noted the financial impact using the administration cost provided by NSW will be lower than the total cost presented in Table 18.

Table 18 Financial impact: assuming 100% inpatient treatment and using AR-DRGI65A

	Assumption	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total drug cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Administration costs							
Hospital admission costs	100% inpatient treatment, using AR-DRG I65A cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost		$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

Source: Table 15, p16 of the Departmental Overview

15. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Circumstances of the application	To note advice provided by the Pharmaceutical Benefits Advisory Committee Economics Subcommittee (PBAC ESC).
Treatment setting (inpatient versus outpatient use)	The applicant proposed that a majority (62%) of use of dinutuximab beta (DB) will be in the outpatient setting with no evidence to support this assumption. The ESC considered that it is likely all patients would be treated as inpatients initially but noted outpatient treatment should not be precluded for the small number of patients that may be able to tolerate it. The ESC considered 100% inpatient use to be a more appropriate assumption to be used in the economic model.
Uncertain treatment effect	The ESC considered the estimated treatment effect for DB + retinoic acid (RA) vs RA alone is based on adjusted and naïve indirect comparisons and is therefore highly uncertain. The ESC noted there is limited clinical data available for the long term infusion (LTI) which the applicant claims will be predominantly used in clinical practice.
Respecify base case to include requested changes from PBAC ESC	The ESC considered it was appropriate to revise the economic model to include (i) 100% inpatient use (ii) cost of administration based on AR-DRG I65A per cycle (which includes the cost of monitoring, AEs and concomitant medications) (iii) Weibull extrapolation of OS. The ESC noted the revised model resulted in an ICER of $**redacted**/ QALY gained and advised this was an appropriate respecified base case for MSAC consideration. The ESC further noted the economic model is based on an uncertain treatment effect (as discussed above).
Differential discounting	The applicant requested a lower discount rate (2%) be applied to the benefits and costs in the economic model, claiming "the incremental life gained by a young person should be valued more highly than that gained by older patients". The ESC noted the MSAC could discuss this issue in the context of what would constitute an acceptable ICER in this patient population, rather than introducing differential discounting.

ESC discussion

The Evaluation Sub-Committee (ESC) noted the circumstances of the application as outlined under Section 2 (Background).

The ESC noted the advice provided by the Pharmaceutical Benefits Advisory Committee Economics Subcommittee (PBAC ESC) on the application, as well as an overview of clinical data presented by the Department. The ESC noted that the submission and the pre-ESC response continued to rely on a matched adjusted indirect comparison (MAIC) to support the claim that dinutuximab beta (DB) + retinoic acid (RA) is superior to RA alone for the treatment of high-risk neuroblastoma (HRNBL). The ESC considered that the treatment effect continued to be highly uncertain.

The submission and pre-ESC response continued to claim that outpatient use is feasible and suggested consultation with overseas clinicians. However, the ESC noted that the relevance of overseas settings to the Australian context is unclear. The submission also suggested a comparison with blinatumomab, which is available as outpatient therapy; however, the ESC

considered that this comparison may be unreasonable, given the different administration and adverse event profiles for DB and blinatumomab. The ESC considered it unlikely patients with HRNBL would be treated with DB in a non-admitted or day admitted setting, although acknowledged outpatient treatment is not precluded and may be possible in a small number of patients for at least part of some treatment cycles. However, the applicant's continued claim that the majority of use of DB will be in the outpatient setting is not supported by the evidence provided.

The ESC noted the risk of serious adverse events associated with DB treatment, as well as limitations in the quality of evidence for safety and effectiveness.

The ESC noted the applicant's claim that the long term infusion (LTI) dosing regimen for HRNBL is associated with improved tolerability and the same treatment effect compared to the short term infusion (STI) regimen, but considered this was inadequately supported.

The ESC noted that the PBAC ESC had suggested a number of changes to parameters in the economic model. Not all of these had been incorporated into the model, and some were included as sensitivity analyses rather than changing the base case:

- Inpatient use: PBAC ESC requested that the base case model should assume that all patients are treated as inpatients for the duration of their treatment. This was included in sensitivity analyses in the updated submission.
- Cost of administration: PBAC ESC considered that use of the Australian Refined Diagnosis Related Group (AR-DRG) for chemotherapy administration (R63Z) was not appropriate. The revised model used alternative AR-DRGs, but ESC considered that the methodology applied to calculate a daily cost was not appropriate.
- Extrapolation method and convergence: PBAC ESC considered that the Gompertz extrapolation function was the least conservative option and favoured DB. The PBAC ESC requested use of the Weibull extrapolation method, but this was provided in sensitivity analyses only. The PBAC ESC also considered that convergence of the curves for overall survival would be appropriate (based on data from Yu 2014), and that some convergence is observed using the Weibull extrapolation method.

The base case incremental cost-effectiveness ratio (ICER) in the submission, without incorporating all the changes requested by the PBAC ESC, was $**redacted**. Multivariate sensitivity analysis that combined all the PBAC ESC's changes resulted in an ICER of $**redacted**. The ESC considered that this multivariate analysis should be considered the respecified base case for MSAC consideration.

Financial and budgetary impacts were also revised by the Department to include 100% inpatient treatment using AR-DRG I65A, resulting in a total cost of $**redacted** million to $**redacted** million per year. The ESC noted that the number of eligible patients and the average number of vials used per patient per course was uncertain.

The ESC noted the applicant's request for a lower discount rate, claiming that "the incremental life gained by a young person should be valued more highly than that gained by older patients". ESC noted that MSAC could discuss this issue in the context of what would constitute an acceptable ICER, rather than introducing differential discounting.
Overall, ESC considered that the updated submission, supplemented with additional economic and financial analyses from the Department, included sufficient details for consideration by MSAC.

16. Other significant factors

Nil

17. Applicant comments on MSAC's Public Summary Document

The Sponsor is pleased with the MSAC recommendation and will work with Government for rapid access to Qarziba for high risk neuroblastoma. The Sponsor wishes to thank MSAC and the Department for their commitment to this vulnerable group of patients.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website