

## 5.04 EFLORNITHINE, Tablet 192 mg (as hydrochloride), Ifinwil<sup>®</sup>, Norgine Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 1 submission requested Authority Required (Written) listing for eflornithine for post-maintenance treatment to prevent relapse in patients with high-risk neuroblastoma (HRNB) who are in remission (i) at the end of upfront therapy; or (ii) after any previous treatment for relapsed or refractory disease.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SOC).

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients aged 1 year and older with high-risk neuroblastoma (HRNB) who have responded to prior multiagent, multimodality therapy: - Stratum 1: Patients who were in remission at the end of upfront therapy <sup>a</sup> - Stratum 2: Patients who were in remission after any previous relapse or refractory therapy <sup>b</sup>
Intervention	Eflornithine oral tablet twice a day for 2 years or until recurrence of disease or unacceptable toxicity occurs (plus standard of care, SOC). The eflornithine dose is determined based on body surface area (BSA). Dose range is 1 to 4 x 250 mg tablets twice a day; tablets may be swallowed whole, chewed, or crushed and mixed with soft food or liquid <sup>c</sup> .
Comparator	SOC defined as follow-up care and monitoring
Outcomes	EFS, OS, safety
Clinical claim	In patients ≥ 1 year old with HRNB, eflornithine + SOC is superior to SOC alone at improving EFS and OS, with a manageable adverse event safety profile.

Source: Table1-1, p18 of the submission.

<sup>a</sup> Defined in Study NMTRC003b as: chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, or anti-ganglioside 2 (GD2) antibody therapy with retinoic acid up to 6 cycles.

<sup>b</sup> Defined as any patient who received additional therapy due to a suboptimal response to standard therapy.

<sup>c</sup> Draft product information (PI) 2024

BSA=body surface area; EFS=event free survival; HRNB=high-risk neuroblastoma; OS=overall survival; PI=product information; SOC=standard of care

### 2 Background

#### Registration status

- 2.1 Eflornithine was granted orphan drug designation by the TGA on 7 December 2022. The submission was made under the TGA/PBAC Parallel Process for the indication: ‘treatment of adults and paediatric patients aged 1 year and older with high-risk neuroblastoma (HRNB) who have responded to prior multiagent, multimodality therapy.’
- 2.2 The TGA used the FDA’s assessment aid in lieu of a TGA Clinical Evaluation Report. A positive TGA Delegate’s Overview was available prior to the ESC meeting. The

Delegate proposed to approve eflornithine with the following conditions of registration:

- 1) Submit to the TGA the same data that were submitted to the FDA regarding a post-marketing requirement to conduct an integrated safety analysis of clinical trial data to assess the serious risk of ototoxicity and to characterise the serious risks of severe adverse reactions including myelosuppression and hepatotoxicity and their sequelae; and to identify risk factors for development of these adverse reactions; and
- 2) Adhere to the Risk Management Plan evaluator recommendations, including implementing the black triangle scheme to report suspected adverse events (AEs) related to new medicines.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### 3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

#### Initial Restriction

MEDICINAL PRODUCT medicinal product pack	DPMQ (published)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EFLORNITHINE					
Eflornithine, 250 mg tablet, 100	\$	3	300	2	Ifinwil
Eflornithine, 250 mg tablet, 100	\$	2	200	2	Ifinwil
Eflornithine, 250 mg tablet, 100	\$	2	200	4	Ifinwil
Eflornithine, 250 mg tablet, 100	\$	1	100	1	Ifinwil
<b>Restriction Summary / Treatment of Concept:</b>					
	<b>Category / Program:</b> <input checked="" type="checkbox"/> General Schedule (Code GE – Schedule 85) Section 100 – Highly Specialised Drugs Program – Public (Code HB)/ Private (Code HS)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (FULL assessment - written)				
	<b>Episodicity:</b> n/a				
	<b>Severity:</b> High-risk				
	<b>Condition:</b> Neuroblastoma				
	<b>Indication:</b> Eflornithine is indicated for the treatment of patients aged 1 year and older with high risk neuroblastoma (HRNB) who have responded to prior multiagent, multimodality therapy. <i>High-risk neuroblastoma</i>				
	<b>Treatment Phase:</b> Initial and Continuing Treatment and Grandfathered arrangements				
	<b>Clinical criteria:</b>				
	Patient must have high risk neuroblastoma according to the <i>least one of the following risk classification system: (i) International Neuroblastoma Risk Group (INRG); or (ii) Children’s Oncology Group (COG); or (iii) International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) risk classification system</i>				

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	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be in remission <del>at the end of upfront therapy for high risk neuroblastoma, with at least a partial response, at the end of multiagent, multimodality therapy including anti-GD2 immunotherapy for high-risk neuroblastoma;</del> OR
	Patient must be in remission after any previous relapse or refractory therapy for high-risk neuroblastoma
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be initiated <del>within 120 days</del> after completing previous therapy
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>Treatment must be ceased on disease progression or on completion of 27 cycles (equivalent to 2 years) of PBS subsidised treatment under this restriction, whichever comes first</del>
	<b>Treatment Criteria:</b>
	<i>Must be treated in a hospital/cancer centre for initial treatment by either a: (i) paediatric oncologist (ii) haematologist;</i>
	<b>AND</b>
	<b>Population criteria:</b>
	Patients aged 1 year and older
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must have body surface area > 0.25 m <sup>2</sup>
	<b>Prescribing Instructions:</b> <del>The definition of remission (NAD = no active disease; NED = no evidence of disease) is defined as requiring an overall response of partial response or better at the end of upfront treatment or after taking at least one previous relapse therapy for relapsed or refractory disease, based on imaging studies and negative for disease in the bone marrow</del>
	<b>Prescribing Instructions:</b> <i>Prior to initiating treatment with Ifinwil, a complete blood count, liver function tests and baseline hearing assessments should be performed and documented in the patients' medical records.</i>
	<b>Prescribing Instructions:</b> <i>At the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' Body Surface Area (BSA), according to the dosing schedule in the TGA approved Product Information. Up to a maximum of 3 packs (containing a total quantity of 300 tablets) and 2 repeats may be authorised under this restriction (providing 3 months of therapy for each prescription).</i>
	<b>Prescribing Instructions:</b> <i>Authority applications for initial treatment must be made in writing and must include: (a) details of the proposed prescription; and (b) a completed PBS authority application form, relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following: (i) Details of prior treatment for high-risk neuroblastoma [dosage, date of commencement and duration of therapy]; and (iii) The patients' BSA measurement</i>
	<b>Administrative Advice:</b> <i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></i>

	Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
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## Continuing Restriction

<b>Restriction Summary / Treatment of Concept:</b>	
	<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Immediate assessment (Telephone/Online)
	<b>Episodicity:</b> n/a
	<b>Severity:</b> High-risk
	<b>Condition:</b> Neuroblastoma
	<b>Indication:</b> High-risk neuroblastoma
	<b>Treatment Phase:</b> Continuing Treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have developed disease progression while receiving treatment with this drug for this condition.
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a total of 27 cycles (based on a 4 weeks per cycle) from the first dose of this drug, regardless of whether it was PBS/non-PBS subsidised
	<b>Prescribing Instructions:</b>
	At the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' Body Surface Area (BSA), according to the dosing schedule in the TGA approved Product Information. With the intention of providing 3 months of therapy for each prescription: up to a maximum of 3 packs (containing a total quantity of 300 tablets) and 2 repeats may be approved.
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

- 3.2 The submission requested an ex-manufacturer price of \$ [REDACTED] per 100 tablets.
- 3.3 The submission relied on a clinical algorithm that divides patients into 2 groups that would both be eligible for treatment with eflornithine: Stratum 1 (described in the restriction as 'Patient must be in remission at the end of upfront therapy for high-risk neuroblastoma') and Stratum 2 (described in the restriction as 'Patient must be in remission after any previous relapse or refractory therapy for high-risk neuroblastoma'). The PBAC considered it would be appropriate to not differentiate Stratum 1 and Stratum 2 patients in the listing and make eflornithine available for patients in remission after receiving multiagent, multimodality therapy, consistent with the proposed TGA indication.

- 3.4 The submission proposed listing of eflornithine 250 mg tablets under four items with different maximum quantities and number of repeats, to provide a sufficient duration of supply for the recommended dosing regimen by body surface area (BSA). However, as there is only one pack-size and dose available, the Secretariat suggested that there should be one listing where the prescriber can adjust the quantity and repeats according to the patient's BSA, in line with the dosage requirements specified in the TGA Product Information (PI).
- 3.5 For each dose, the requested maximum quantity and number of repeats provides for 100 to 112 days' (at least 3 months) supply. The draft PI recommends that in growing children, change in BSA should be assessed every 3 months from initiation of treatment and the dose adjusted accordingly. The Secretariat suggested a cap on the limit be enforced as a Prescribing Instruction (i.e. 300 tablets with 2 repeats) to align with the proposal that each prescription be reflective of 3 months of therapy.
- 3.6 The submission requested Section 85 Authority Required (In Writing) listing of eflornithine for patients with HRNB who have responded to prior multiagent, multimodal therapy. Given that neuroblastoma is a rare type of cancer where patients require specialised care and close monitoring for dosing, the Secretariat considered that a Section 100 Highly Specialised Drugs (HSD) Program listing may be more appropriate than a Section 85 listing.
- 3.7 According to the request, patients must:
- (i) Be aged 1 year and older with  $BSA > 0.25 \text{ m}^2$ ; the Secretariat noted that it may be appropriate for the restriction to be age agnostic because patients must receive a substantial amount of prior induction/ consolidation/ maintenance therapy, over a period of approximately 18 months, before receiving treatment with eflornithine.
  - (ii) Be in remission either following upfront therapy or after any previous relapse or refractory to therapy.
  - (iii) Initiate treatment within 120 days of previous treatment; the Secretariat noted that this criterion may be either unnecessary (given that most families are motivated to commence eflornithine as soon as possible), or unduly restrictive (given that some patients may be excluded from treatment despite being in remission).
  - (iv) Cease treatment on disease progression or on completion of 27 cycles (equivalent to 2 years) of treatment, whichever comes first; the Secretariat noted that patients in the pivotal Study 3b who had a treatment interruption went on to complete 27 4-weekly cycles of eflornithine (in addition to any treatment interruptions), and therefore this criterion has been amended to ensure treatment interruptions are not counted towards the total number of cycles or 2-year timeframe.

- 3.8 The proposed restriction defined ‘high-risk’ disease according to the Children’s Oncology Group (COG) or International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) risk classification systems and ‘remission’ as requiring an overall response of partial response or better to previous treatment based on imaging studies plus being negative for disease in bone marrow. The Secretariat noted that risk classification systems are subject to change over time, and HRNB is a rare disease treated by specialist paediatric oncologists and therefore misclassification is unlikely.
- 3.9 The ESC indicated that the restriction should be age agnostic, rather than  $\geq 1$  year, as prior induction/ consolidation/ maintenance therapy typically occurs over a period of approximately 18 months before patients would receive treatment with eflornithine.
- 3.10 The submission requested a single agnostic phase restriction to cover the initial and continuing treatment phases. The Secretariat suggested that splitting the restrictions to an initial and continuing phases may be required. The Secretariat noted that the submission did not propose any specific response or assessment criteria for continuing treatment with eflornithine after initiating treatment. As there is no assessment needed for the response criteria, the stopping rule would be disease progression or a total of 2 years (27 cycles) of treatment (excluding treatment breaks).
- 3.11 The submission stated that a grandfathering restriction would be necessary but did not propose any specific criteria. In July 2024, the Australian Government implemented an early funding pathway for eflornithine in HRNB (Butler 2024a<sup>1</sup>). This one-off funding scheme continued until the sponsor’s Expanded Access Program (EAP) was established in October 2024 (Butler 2024b<sup>2</sup>). It was anticipated in the submission that approximately < 500 patients would be grandfathered from the EAP, accounted for in the financial estimates.
- 3.12 The wording of the requested restriction would likely permit re-treatment of patients for any subsequent periods of remission following disease relapse. The submission stated that the sponsor does not expect that a patient who uses eflornithine in their first remission would use it again in a subsequent remission. Considering the poor prognosis of relapsed patients, however, it is plausible that clinicians may consider prescribing eflornithine in patients who had previously used it. The submission did not present any evidence for the repeated use of eflornithine and the economic model assumed ‘once in a lifetime’ use. The Pre-Sub-Committee Response (PSCR) requested that wording is not added to the restriction that may prevent a second course and

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<sup>1</sup> The Hon Mark Butler MP. 2024. Hope for children with neuroblastoma as Government provides free access to DFMO. Media release. Department of Health and Aged Care. Available at: [Hope for children with neuroblastoma as Government provides free access to DFMO | Health Portfolio Ministers | Australian Government Department of Health and Aged Care](#)

<sup>2</sup> The Hon Mark Butler MP. 2024. Ensuring access to rare cancer treatment for patients with neuroblastoma. Media release. Department of Health and Aged Care. Available at: [Ensuring access to rare cancer treatment for patients with neuroblastoma | Health Portfolio Ministers | Australian Government Department of Health and Aged Care](#)

would prefer to include wording to state that re-treatment would be possible if the clinical need arose.

- 3.13 The requested restriction nominated medical practitioners as the prescriber type. The Secretariat noted that at the stage of eflornithine treatment, most patients are treated by a paediatric oncologist in a cancer centre and regional patients would likely be treated by a GP under supervision of a paediatric oncologist.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 Neuroblastoma is the most common extracranial solid tumour occurring in childhood with 90% of cases being diagnosed before 5 years of age (Youlden 2020<sup>3</sup>). The most common site is the adrenal glands, though tumours can develop anywhere within the sympathetic nervous system from the neck to the pelvis. Approximately half of patients present with metastatic disease, commonly in the bone marrow, liver or skin. The tumours vary greatly in clinical presentation and prognosis. Some tumours are associated with substantial morbidity, while others spontaneously and completely regress.
- 4.2 Neuroblastoma is categorised as low-, intermediate- or high-risk. Risk stratification incorporates age, stage, histology and tumour biology, and informs prognosis and treatment. Neuroblastoma does not inevitably progress from low- to high-risk, and the divergent genomics and biology of the various risk groups suggest they are clinically and biologically different diseases (Youlden 2020). Approximately 50 Australian children are diagnosed with neuroblastoma each year, of which 20-25 are classified as having HRNB (ANZCHOG 2024<sup>4</sup>).
- 4.3 Diagnosis and risk classification of neuroblastoma for the pivotal Study 3b was based on the International Neuroblastoma Staging System (INSS), which was developed in 1986. High-risk disease in Study 3b was determined by the risk classification system devised by COG in 2000, based on the INSS. The INSS determined stage, based on observations during surgery and in the research setting, has been largely replaced by the International Neuroblastoma Risk Group Staging System (INRGSS), which was developed in 2005 and uses results from imaging as well as prognostic factors to determine stage (Irwin 2021<sup>5</sup>). In contrast, the proposed restriction in the submission

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<sup>3</sup> Youlden DR, et al. Incidence and outcomes of neuroblastoma in Australian children: A population-based study (1983-2015). *J Paediatr Child Health*. 2020 Jul;56(7):1046-1052. doi: 10.1111/jpc.14810.

<sup>4</sup> Australian and New Zealand Children's Haematology/Oncology Group [ANZCHOG]. 2024. ANZCHOG Solid Tumour Group position on Eflornithine (DFMO) for patients with high-risk neuroblastoma (HR-NB) in Australia and New Zealand. Available at: [Eflornithine-DFMO-use-for-patients-with-high-risk-neuroblastoma-in-Australia-and-New-Zealand-v1.0-12.07.2024.pdf](#)

<sup>5</sup> Irwin, M. et al., Revised Neuroblastoma Risk Classification System: A Report From the Children's Oncology Group. *JCO* 39, 3229-3241(2021). DOI:10.1200/JCO.21.00278

defined 'high-risk' disease according to the current COG or SIOPEN risk classification systems. The SIOPEN system was developed from the SIOPEN High-Risk Neuroblastoma Study, which began in 2007 and included various risk classifications.

- 4.4 The treatment of neuroblastoma varies depending on the risk category. Low-risk disease may be managed with observation or surgery (Bagatell 2023<sup>6</sup>). Intermediate-risk disease is generally managed with lower intensity chemotherapy with or without surgery. High-risk disease is typically managed with an aggressive multimodality approach including (i) intensive induction multiagent chemotherapy and surgery, followed by (ii) consolidation therapy including high-dose chemotherapy, autologous stem cell transplant (ASCT) and radiation therapy, then (iii) post-consolidation or maintenance therapy with immunotherapy (ANZCHOG 2024). Survival has improved in recent years; 5-year survival rates for low-, intermediate- and high-risk diseases are approximately 98%, 95% and 62%, respectively (Irwin 2021). Approximately 80% of HRNB patients respond to upfront therapy (with 20% being refractory) but relapse remains common in HRNB, particularly for children aged >18 months at diagnosis (DuBois 2022<sup>7</sup>, Youlden 2020). Approximately 50% of patients relapse, and the prognosis in relapsed and refractory patients is poor.
- 4.5 Under the proposed treatment algorithm, treatment with eflornithine is proposed for post-maintenance therapy to prevent relapse in patients with HRNB who have responded to prior multiagent, multimodality therapy and are in remission. This includes treatment after 'upfront' therapy (i.e. induction, consolidation and maintenance) as well as treatment following any previous treatment for refractory or relapsed disease. Patients taking eflornithine would continue to receive the standard follow-up care and monitoring recommended for HRNB.
- 4.6 Eflornithine hydrochloride (also known as difluoromethylornithine [DFMO]) is a structural analogue of ornithine. It acts as a specific and irreversible suicide inhibitor (an irreversible form of enzyme inhibition) of the ornithine decarboxylase (ODC), an enzyme that controls the synthesis of polyamines, which exist in all living cells. Inhibition of ODC activity interrupts polyamine synthesis and results in inhibition of growth and cell differentiation in a number of malignant and non-malignant mammalian cells, and has been shown to inhibit the promotion and progression phases of carcinogenesis.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

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<sup>6</sup> Bagatell R, DuBois SG, Naranjo A, et al. Children's Oncology Group's 2023 blueprint for research: Neuroblastoma. *Pediatr Blood Cancer*. 2023; 70(Suppl. 6):e30572. <https://doi.org/10.1002/pbc.30572>

<sup>7</sup> DuBois, S.G. et al., High-Risk and Relapsed Neuroblastoma: Toward More Cures and Better Outcomes. *Am Soc Clin Oncol Educ Book* 42, 768-780(2022). DOI:10.1200/EDBK\_349783

## 5 Comparator

- 5.1 The submission nominated standard of care (SOC), defined as follow-up and monitoring, as the main comparator. The main arguments provided in support of this nomination were that there are no approved therapies designated for post-maintenance treatment for patients with HRNB, and there are no near market comparators. Eflornithine would not replace any medicine, and would be used in addition to current SOC.
- 5.2 The evaluation considered that this choice of comparator was appropriate, however noted that the evidence presented for eflornithine is from a single-arm study and the evidence for SOC as the comparator is from historical controls.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease including the challenges faced by patients and their families, and how eflornithine would be used in practice. The clinician referred to treatment of both Stratum 1 and Stratum 2 patients with eflornithine, noting that clinical data for the latter group had been submitted to regulatory agencies as part of the drug approval process but had not yet been published in a peer reviewed journal. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (262), health care professionals (3) and organisations (5) via the Consumer Comments facility on the PBS website.
- 6.3 The Australian and New Zealand Children's Haematology/ Oncology Group (ANZCHOG) Solid Tumour Group described neuroblastoma as one of the most challenging childhood cancers that accounts for a significant proportion of paediatric cancer mortality in Australia. It supported the listing of eflornithine on the PBS, describing it as a critical therapy that requires equitable and timely access.
- 6.4 The National Paediatric Medicines Forum (NPMF) stated that the PBS listing of eflornithine will be immensely beneficial to all relevant paediatric patients diagnosed with HRNB as well as improving equitable access and outcomes for all stakeholders. The NPMF reported the usage of eflornithine in children's hospitals in some Australian states. Children's Healthcare Australasia, as part of the NPMF, submitted a separate statement describing the background of HRNB treatment in Australia, costs of treatment, prior federal government funding, FDA summary of efficacy and outcomes, and ANZCHOG criteria on population and treatment. The NPMF reiterated the

ANZCHOG estimate that there are approximately 50 children diagnosed with neuroblastoma each year and 20 to 25 are classified as having HRNB.

- 6.5 The Neuroblastoma Australia charity described the devastating nature of HRNB. It commented on the improved survival associated with eflornithine by preventing relapse in the context of the current relapse rate of 50% after upfront therapy. It emphasised that once a child relapses, the options are very limited and only a small proportion of children are able to re-enter remission.
- 6.6 Rare Cancers Australia described the side effects and long hospital stays associated with intense up front therapy. It emphasised the advantages of eflornithine in preventing relapse and the accessibility of an oral medicine for children so that they do not have to return home from hospital with a port for drug administration.
- 6.7 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the eflornithine submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of Study 3b. The PBAC noted that the MOGA classified eflornithine with a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) grade ‘A’, categorising it as a new treatment with substantial benefit in the curative setting.<sup>8</sup>
- 6.8 The comments from health care professionals (HCPs) emphasised that eflornithine reduces the risk of relapse in children with HRNB.
- 6.9 The individuals who commented comprised parents/partners of a current/potential eflornithine patient (39) and other interested individuals (223). The consumer input emphasised the high burden of disease and suffering associated with HRNB, as well as the prohibitive cost of eflornithine. Comments described eflornithine as a treatment that could reduce the risk of relapse and reduce the need for further harsh and potentially life-threatening treatments, allowing patients to have normalcy and better quality of life. The comments discussed side effects such as hearing loss, dry skin, hair thinning, as being minimal or manageable compared with side effects experienced during up front treatment.

### ***Clinical studies***

- 6.10 The submission was based on:
- (i) Study 3b, a single-arm study of eflornithine in post-maintenance treatment of HRNB patients in remission at the end of upfront therapy (Stratum 1) or after therapy for refractory/relapsed disease (Stratum 2). Study 3b compared the single arm data for eflornithine to historical controls from Study ANBL0032 (for Stratum 1 patients) and Santana 2008 (for Stratum 2 patients).<sup>9</sup>

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<sup>8</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

<sup>9</sup> For information on Study ANBL0032 and Santana 2008, see footnote to Table 3.

- (ii) A propensity-score matching (PSM) study, comparing outcomes in Study 3b (Stratum 1 patients only) to external controls treated with SOC, who were selected from the single-arm phase of Study ANBL0032.

- 6.11 The protocol for the PSM study was developed with input from the FDA. The FDA recommended that the Sponsor undertake a blinded independent central review (BICR) of the imaging for the patients from Study 3b that were to be included in the PSM. At a pre-New Drug Application (NDA) meeting in 2021, the FDA stated that the comparison with Study ANBL0032 appeared acceptable to support an NDA review, however, the FDA would rely on an overall assessment of multiple independent analyses, including additional analyses recommended by the FDA (Duke 2024<sup>10</sup>).
- 6.12 The submission excluded Study 14 (NCT02679144), an ongoing ‘confirmatory study’ of eflornithine as post-maintenance therapy in HRNB. Completion of data collection for the primary outcome is expected in February 2028. The submission did not provide any data from Study 14; however, the FDA safety assessment was based on a pooled safety population from Study 3b (n=85) and Study 14 (n=259) (Centre for Drug Evaluation and Research [CDER] 2021<sup>11</sup>) (see paragraph 6.30 below).
- 6.13 Details of the studies presented in the submission are provided in Table 2.

**Table 2: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Study 3b NMTRC003b NCT02395666	A Phase II Preventative Trial of DFMO (Eflornithine HCl) as a Single Agent in Patients With High Risk Neuroblastoma in Remission Sholler GLS, Ferguson W, Bergendahl G, Bond JP, Neville K, Eslin D, Brown V, Roberts W, Wada RK, Oesterheld J, Mitchell D, Foley J, Parikh NS, Eshun F, Zage P, Rawwas J, Sencer S, Pankiewicz D, Quinn M, Rich M, Junewick J, Kraveka JM. Maintenance DFMO Increases Survival in High Risk Neuroblastoma.	Clinical Study Report. Final. September 2024.  Sci Rep. 2018 Sep 27;8(1):14445. doi: 10.1038/s41598-018-32659-w.
Propensity Score Matching (PSM) Study	Comparison of Study 3b to Study ANBL0032 External Control Database Eflornithine (DFMO) Javier Oesterheld et al., Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score–Matched Survival Outcome Comparisons.	Clinical Study Report. Final. September 2024.  JCO 42, 90-102(2024). DOI:10.1200/JCO.22.02875

Source: Table 2-4, pp65-66 of the submission.

- 6.14 The key features of the studies are summarised in Table 3.

<sup>10</sup> Duke ES, et al. US Food and Drug Administration Approval Summary: Eflornithine for High-Risk Neuroblastoma After Prior Multiagent, Multimodality Therapy. J Clin Oncol. 2024 Sep 1;42(25):3047-3057. doi: 10.1200/JCO.24.00546.

<sup>11</sup> Center for Drug Evaluation and Research. 2021. Multi-Discipline Review. Application number: 21550Orig1s000. July 2021. Available at: [Review](#)

**Table 3: Key features of the included evidence**

Study	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
<b>STRATUM 1 AND 2: Eflornithine + SOC versus SOC (via unadjusted comparison to historical controls)</b>						
Study 3b: NMTRC003/003b (NCT02395666)  Enrolled June 2012 to Feb 2016.	N = 147 <sup>a</sup> (Stratum 1 n=105) (Stratum 2 n=35)	P2, single arm (preventative), MC, OL, historical control arm (ANBL0032 <sup>c</sup> and Santana 2008 <sup>d</sup> )  Mean follow-up 5.9yrs (Stratum 1), 4.4yrs (Stratum 2).	High	Patients (≤21 years) with HRNB in remission at end of upfront therapy (Stratum 1), or after any previous relapse or refractory therapy (Stratum 2).	Primary: EFS Secondary: OS (Stratum 1 only), safety	Yes (Stratum 2 only)
<b>STRATUM 1: Eflornithine + SOC versus SOC (via adjusted comparison to historical controls)</b>						
PSM Study - Study 3b (Stratum 1) vs Study ANBL0032 <sup>c</sup> (single-arm, open-label phase, enrolled Apr 2009 to Jul 2015)	Base case (3:1 matched) n = 90 Study 3b (eflornithine+SOC) n = 270 ANBL0032 (SOC)	PSM <sup>b</sup> analysis, Study 3b (eflornithine+SOC) vs Study ANBL0032 <sup>c</sup> (SOC).  Median follow up: 6.1 yrs (eflornithine+SOC), 5 yrs (SOC)	Unclear	Patients (<31 years) with HRNB in remission after receiving upfront therapy (Stratum 1)	Primary: EFS Secondary: OS	Yes (Stratum 1 and 2)

Source: NMTRC003B Eflornithine CSR and 3bvANBL0032: Comparison of HRNB Study 3b to ANBL0032 External Control Database Eflornithine (DFMO).

COG = Children's Oncology Group; EFS = event-free survival; HRNB = high-risk neuroblastoma; MC = multi-centre; OL = open label; OS = overall survival; PSM = propensity score-matched; P2 = phase 2; SOC = Standard of Care; Stratum 1 = Patients who were in remission at the end of upfront therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, or anti-ganglioside 2 (GD2) antibody therapy with retinoic acid up to 6 cycles; Stratum 2 = Patients who were in remission after any previous relapse or refractory therapy (defined as any patient who received additional therapy due to a suboptimal response to standard therapy);

<sup>a</sup> The trial enrolled 147 patients, five patients were screen failures, stratum determination was missing for one patient and one subject was enrolled with an eligibility waiver and prospectively planned for exclusion from efficacy analyses, resulting in 140 participants providing efficacy data (ITT set) and 101 participants providing safety data (Safety set) (p48 of the NMTRC003B Eflornithine CSR).

<sup>b</sup> Propensity-score matching was implemented to balance eflornithine and no eflornithine patients according to 11 baseline covariates: age at high-risk diagnosis, sex, race, stage at HRNB diagnosis per the 1993 International Neuroblastoma Staging System (categories of 4 or <4 including 4S), pre-ASCT response, transplant type, time from ASCT to start of immunotherapy, duration of immunotherapy, overall response at immunotherapy end, time from diagnosis to immunotherapy end, and MYCN (exact matching: amplified/nonamplified).

<sup>c</sup> ANBL0032 (NCT00026312) was a large phase III partially randomised open-label trial in HRNB patients (0 to <31 years). Patients were randomised to an induction regimen of isotretinoin alone (Regimen A), or isotretinoin plus sargramostim (granulocyte-macrophage colony-stimulating factor), dinutuximab and aldesleukin (interleukin-2) (Regimen B). Following completion of enrolment of the randomised phase of the study, enrolment continued under a single-arm, open-label phase of the study, with all patients receiving the investigational treatment combination (Regimen B) (Desai 2022<sup>12</sup>).

<sup>d</sup> Santana 2008 was a retrospective single centre study investigating disease-free survival, post-recurrence survival intervals and disease control intervals in patients with HRNB treated with one of three institutional protocols between 1991 and 2002, with the aim of establishing reference points for the evaluation of new agents.

<sup>12</sup> Desai, A. V., et al (2022). "Outcomes Following GD2-Directed Postconsolidation Therapy for Neuroblastoma After Cessation of Random Assignment on ANBL0032: A Report From the Children's Oncology Group." J Clin Oncol 40(35): 4107-4118.

## STRATUM 1 AND STRATUM 2 PATIENTS

### Study 3b: Eflornithine + SOC versus SOC (via unadjusted comparison to historical controls)

- 6.15 Study 3b was a phase 2, open-label, multicentre, single-arm study evaluating the efficacy (preventative activity) and safety of eflornithine as a single agent in patients (0-21 years at diagnosis) with HRNB in remission after completion of (i) standard upfront first-line multiagent multimodality therapy (Stratum 1) or (ii) therapy for refractory/relapsed disease (Stratum 2). Remission was defined as at least a partial response (by computerised tomography [CT] or magnetic resonance imaging [MRI]) at the end of immunotherapy evaluation with no evidence of disease in the bone marrow. Patients were enrolled in Study 3b up to 120 days after completion of immunotherapy and eflornithine was initiated at a median 1.2 months from the last dose of retinoic acid. Patients received eflornithine for 2 years (excluding treatment breaks) or until disease recurrence or unacceptable toxicity, plus SOC. The primary endpoint of Study 3b was event-free survival (EFS).
- 6.16 Study 3b was initiated in 2012 under study protocol and database NMTRC003, but due to a change in drug supplier, the study protocol and corresponding database was amended to NMTRC003b in December 2014 (amendment 5). Data in the original NMTRC003 database were not available to the Sponsor. A chart review (BCC001) was conducted to obtain demographic, disease characteristics and EFS and overall survival (OS) outcomes for patients who only received eflornithine prior to amendment 5 (n=40), however no safety data were available for this group. Safety data are only available for direct enrollers and transfer patients from the time of transfer to Study 3b (n=101).
- 6.17 In the absence of a randomised comparator arm, Study 3b included unadjusted comparisons to event rates with SOC in two historical cohorts:
- For Stratum 1 (patients in remission after upfront therapy), the study compared EFS and OS event rates at 2-years for patients treated with eflornithine (from the start of post-maintenance treatment) to event rates for patients treated with SOC (from the start of maintenance treatment) in the randomisation phase of Study ANBL0032 (patients randomised to immunotherapy, n=113), as reported in Yu et al 2010<sup>13</sup>.
  - For Stratum 2 (patients in remission after previous relapse/refractory therapy), the study compared EFS at 2-years (from the start of post-maintenance treatment) for patients treated with eflornithine to a derived event rate for patients treated with SOC (from the start of maintenance treatment, Santana et al 2008<sup>14</sup>). In this

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<sup>13</sup> Yu AL, et al; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med*. 2010 Sep 30;363(14):1324-34. doi: 10.1056/NEJMoa0911123.

<sup>14</sup> Santana, V. M., W. L. Furman, L. M. McGregor and C. A. Billups (2008). "Disease control intervals in high-risk neuroblastoma." *Cancer* 112(12): 2796-2801.

retrospective single centre study, 90 patients with HRNB were treated between 1991 and 2002 at a children's research hospital in the USA, according to one of three institutional frontline protocols between 1991 and 2002. The EFS for SOC was estimated as 10.3% at 2 years (rounded down to 10%), based on the median disease control intervals for patients with first or second recurrence and assuming two thirds of patients would be in first recurrence.

- 6.18 The evaluation considered that unadjusted comparisons to historical controls, presented in Study 3b, were prone to a high degree of bias, given there was no control for differences in the populations or index date. For example, Study 3b reported outcomes for patients treated with eflornithine who had been in remission after completion of upfront therapy or relapse/refractory therapy, whereas Study ANBL0032 and Santana 2008 reported outcomes from an earlier time point in the disease pathway and included patients who did not achieve remission; this comparison likely favours eflornithine.

### **STRATUM 1 PATIENTS**

#### **PSM study: Eflornithine + SOC versus SOC (via adjusted comparison to historical controls)**

- 6.19 The PSM study was undertaken by the Sponsor to more rigorously compare outcomes from Study 3b (Stratum 1) using patient-level data for SOC from Study ANBL0032. The statistical analysis plan for the PSM was developed with input from the FDA:
- Selection criteria were applied to identify patients (i) enrolled in Study 3b (Stratum 1, N=105) who would have met eligibility criteria for Study ANBL0032 and received maintenance treatment according to the Study ANBL0032 protocol, or (ii) enrolled in Study ANBL0032 (N=1,328), would have met eligibility criteria for Study 3b, but were not enrolled in Study 3b. The index date (time zero) used in the analysis for both groups was the date of last immunotherapy, and several comparison cohorts were identified from each study using slightly different selection criteria. Due to overlapping enrolment timelines for Study 3b and Study ANBL0032, some patients who participated in Study ANBL0032 subsequently participated in Study 3b (n=87) and were excluded from the analysis.
  - Propensity scores (PS) were then calculated using a logistic regression model controlling for the following baseline covariates:
    - age at HRNB diagnosis
    - sex
    - race
    - INSS stage at HRNB diagnosis
    - pre-ASCT response
    - transplant type
    - time from ASCT to start of immunotherapy
    - duration of immunotherapy
    - overall response at end of immunotherapy.

Patients with similar PS scores from each study were included in the analysis (i.e. outliers were excluded), and patients were matched 1:3 (eflornithine: no eflornithine) based on a greedy nearest neighbour matching of PS plus exact matching on myelocytomatosis viral oncogene neuroblastoma (MYCN) category (amplified/not amplified).

- After matching, covariate balance was assessed using standardised differences ( $\pm 0.1$ ) and adjustments to the matching algorithm were made when adequate balance was not achieved. The matched groups were then compared for EFS and OS using an unadjusted Cox proportional hazards model controlling only for treatment (eflornithine versus no eflornithine).
- 6.20 The base case in the PSM analysis matched treated patients in the 'Eflornithine PER COG – complete case' cohort (n=91) to control patients in the 'NO eflornithine – complete case' cohort (N=516). All patients received the same upfront therapy as per the COG protocol and complete case was defined as patients with no missing covariates, resulting in 90 treated patients matched to 270 control patients. The evaluation and the ESC noted that the groups were well balanced across the selected covariates both before and after the PSM.
- 6.21 Despite matching on a variety of patient characteristics and index date, the adjusted comparisons presented in the PSM study were considered by the evaluation to have a moderate degree of bias. Several factors related to patient clinical profile or their care were unable to be included in the PSM algorithm as data were not available (in either one or both databases), including: neuroblastoma histology, number of immunotherapy cycles, socio-economic status, insurance status, geographic location, patient travel distance to study sites, surgery for tumour removal and end-consolidation response. While post-hoc analyses have shown that the study populations were generally similar for some variables not included as covariates in the PSM, the impact of residual confounding resulting from unmeasured covariates was unknown. The evaluation noted that results of the PSM study should be interpreted in this context. In addition, some patients were excluded prior to PSM either (i) due to selection criteria to align the two patient populations in Study 3b and ANB0032 or (ii) due to missing data.

## Comparative effectiveness

### STRATUM 1 AND STRATUM 2 PATIENTS

#### Study 3b: Eflornithine + SOC versus SOC (via unadjusted comparison to historical controls)

Table 4 and Figure 1 present EFS and OS in Study 3b for Stratum 1 and Stratum 2 myelocytomatosis

	Stratum 1			Stratum 2		
	Eflornithine (N=105)	Historical control <sup>a</sup>	p-value	Eflornithine (N=35)	Historical control <sup>b</sup>	p-value
<b>EFS</b>						
Patients with event n/N (%)	NR	-	-	NR	-	-
Median EFS months (95% CI)	NE	-	-	NE	-	-
KM EFS at 24 months	0.85	0.70	0.0021	0.46	0.10	<0.0001
KM EFS at 48 months	0.83	0.60	<0.0001	0.46	0.10	<0.0001
<b>OS</b>						
Patients with event n/N (%)	NR	-	-	NR	-	-
Median OS months (95% CI)	NE	-	-	NR	-	-
KM OS at 24 months	0.97	0.85	0.003	0.80 <sup>c</sup>	NR	NR
KM OS at 48 months	0.95	0.75	0.0001	0.62 <sup>c</sup>	NR	NR

Source: Tables 2.26, 2.27, 2.30 and 2.31, pp 109-110, 121-122 of the submission; Figures 2.14 and 2.15, p115 of the submission and Figure 3-26, p205 of the submission.

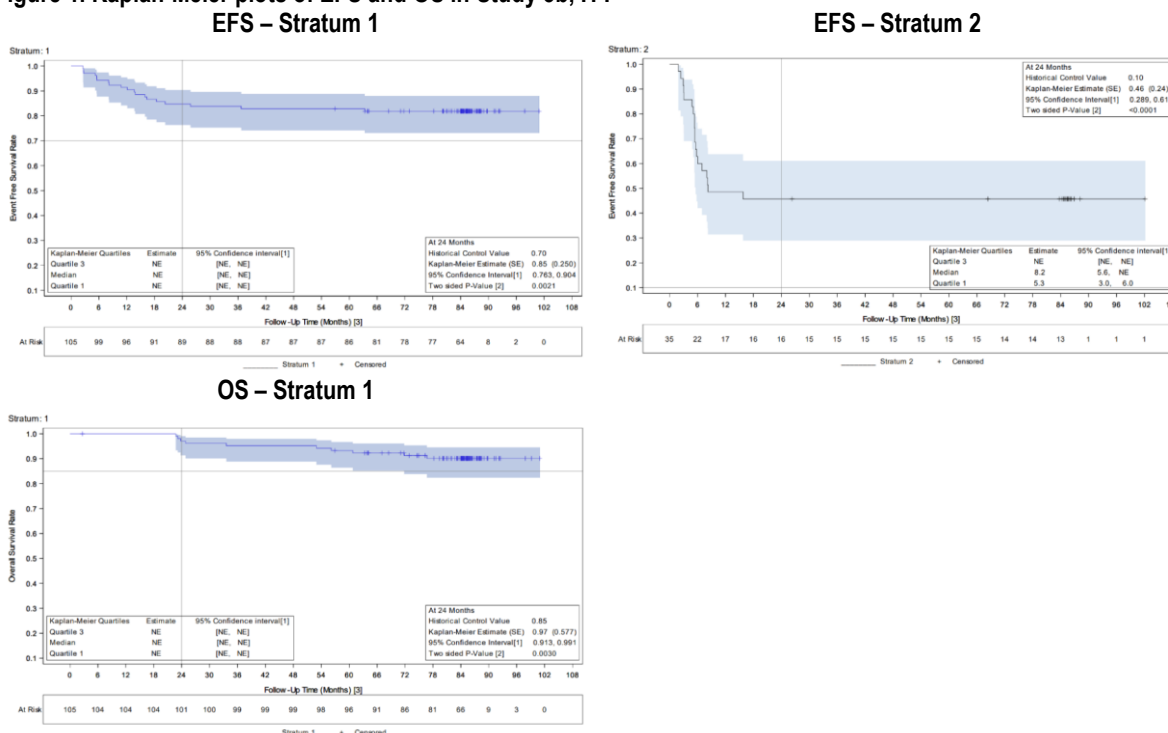
EFS=event free survival; KM=Kaplan-Meier estimate; NE=not estimable; NR=not reported; OS=overall survival.

<sup>a</sup> Stratum 1 historical control estimates were derived from Study ANBL0032 (Yu et al 2010)

<sup>b</sup> Stratum 2 historical control estimates were derived from Santana et al 2008

<sup>c</sup> Based on data reported in the modelled economic evaluation; OS for Stratum 2 was not a pre-specified outcome in the Study 3b protocol and was not reported in the CSR.

Figure 1. Kaplan-Meier plots of EFS and OS in Study 3b, ITT



Source: Figures 2.9, 2.10 and 2.22 pp 109-110, 122 of the submission.

EFS=event free survival; ITT=intention-to-treat; OS=overall survival.

6.22 The results for Study 3b showed that EFS and OS were significantly higher for patients treated with eflornithine compared to the estimated rates for historical controls treated with SOC. In Stratum 1, the EFS rate at 48 months was 83% for treated patients compared to 60% for the historical controls ( $p < 0.0001$ ), and the OS rate was 95% for treated patients compared to 75% for the historical controls ( $p = 0.0001$ ). In Stratum 2, the EFS rate at 48 months was 46% for treated patients compared to 10% for the historical controls ( $p < 0.0001$ ). The evaluation considered that the results of the unadjusted comparisons to historical controls should be interpreted with caution, given the differences in the index dates and potential for uncontrolled or residual confounding.

### STRATUM 1 PATIENTS

#### PSM study: Eflornithine + SOC versus SOC (via adjusted comparison to historical)

6.23 Table 5 and Figure 2 present EFS and OS in the base case analysis of the PSM primary study (Stratum 1 patients).

Table 5: Summary of EFS and OS in PSM primary analysis <sup>a</sup>

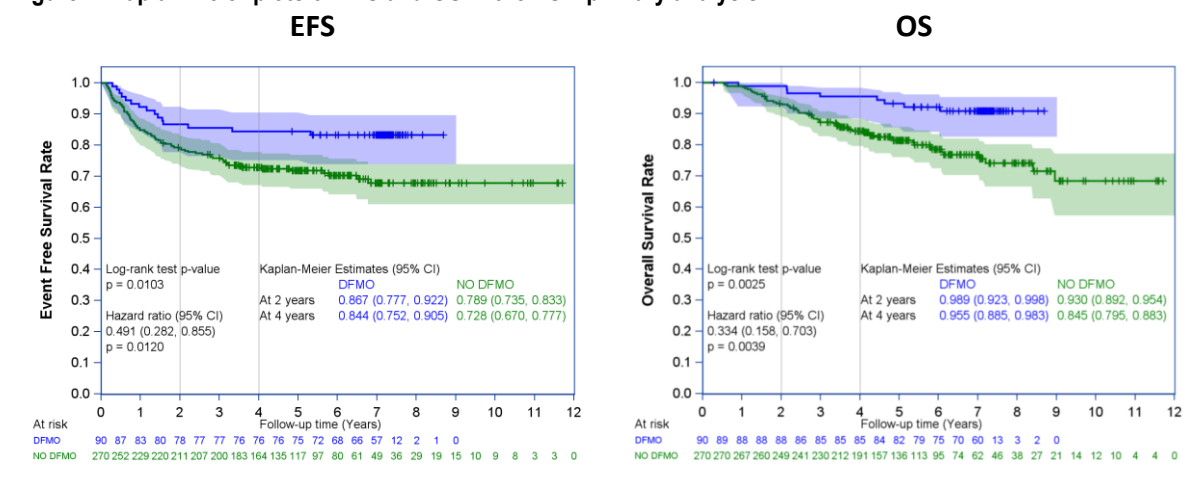
	Eflornithine	Standard of Care	HR (95% CI)
<b>EFS</b>			
Patients with event n/N (%)	15/90 (16.7%)	79/270 (29.3%)	
Median EFS months (95% CI)	NE	NE	
KM EFS at 24 months	0.867 (0.777, 0.922)	0.789 (0.735, 0.833)	<b>0.49 (0.28, 0.86)</b>
KM EFS at 48 months	0.844 (0.752, 0.905)	0.728 (0.670, 0.777)	
KM EFS at 84 months	0.833 (0.739, 0.896)	0.678 (0.609, 0.738)	
<b>OS</b>			
Patients with event n/N (%)	NR	NR	
Median OS months (95% CI)	NE	NE	
KM OS at 24 months	0.989 (0.923, 0.998)	0.930 (0.892, 0.954)	<b>0.33 (0.16, 0.70)</b>
KM OS at 48 months	0.955 (0.885, 0.983)	0.845 (0.795, 0.883)	
KM OS at 84 months	NR	NR	

Source: Table 2.29, p116 of the submission;

CI=confidence interval; COG = Children's Oncology Group; EFS=event free survival; HR=hazard ratio; KM=Kaplan-Meier estimate; NE=not estimable; NR=not reported; OS=overall survival; PSM=propensity score matched.

<sup>a</sup> Eflornithine PER COG – complete case vs NO Eflornithine – complete case, matched 1:3.

Figure 2. Kaplan-Meier plots of EFS and OS in the PSM primary analysis



Source: Figures 2.16 and 2.17, p117 of the submission

EFS=event free survival; OS=overall survival; PSM = propensity score-matched.

- 6.24 The results of the PSM study found a statistically significant improvement in EFS (hazard ratio [HR] = 0.49, 95% Confidence interval [CI]: 0.28, 0.86) and OS (HR = 0.33, 95%CI: 0.16, 0.70) in the base case analysis.
- 6.25 Multiple sensitivity and supplementary analyses were conducted, evaluating the impact of potential bias related to the study design and assumptions. These included alternative analysis populations and selection criteria, alternative matching methods, covariate and index date modifications, as well as comparisons without matching. Overall, the results of the sensitivity analyses were generally consistent with the base case analysis with a few exceptions.
- 6.26 Overall, the evaluation noted that the results of the PSM study estimated a relatively large treatment effect favouring eflornithine but the confidence intervals were wide and the point estimates varied somewhat in terms of magnitude across the sensitivity analyses.

## Comparative harms

### STRATUM 1 AND STRATUM 2 PATIENTS

#### Study 3b: Eflornithine + SOC versus SOC (via unadjusted comparison to historical controls)

- 6.27 Table 6 summarises key AEs reported in Study 3b. As the original Study NMTRC003 did not collect safety data, results are only available for treatment during Study 3b. Patients enrolled directly into Study 3b (n=41) contributed safety data from the start of enrolment, whereas patients transferred from Study NMTRC003 into Study 3b (n=44) only contributed safety data from the point of transfer.

**Table 6: Summary of key adverse events in Study 3b**

	Stratum 1		Stratum 2	
	Direct (N=41)	Direct + Transfers (N=85)	Direct (N=11)	Direct + Transfers (N=16)
Total AEs, n	251	363	39	59
<b>Patients with at least one AE, n (%)</b>				
Any AE	33 (80.5)	63 (74.1)	9 (81.8)	14 (87.5)
Any SAE	6 (14.6)	10 (11.8)	0	1 (6.3)
Treatment related AE	16 (39.0)	25 (29.4)	3 (27.3)	5 (31.3)
Treatment related SAE	1 (2.4)	2 (2.4)	0	0
Worst severity - Grade 2 AE	14 (34.1)	30 (35.3)	7 (63.6)	11 (68.8)
Worst severity - Grade 3 AE	18 (43.9)	31 (36.5)	2 (18.2)	3 (18.8)
Worst severity - Grade 4 AE	1 (2.4)	2 (2.4)	0	0
AE leading to dose modification	5 (12.2)	7 (8.2)	0	0
AE leading to interruption / discontinuation	8 (19.5)	9 (10.6)	1 (9.1)	2 (12.5)
<b>AEs reported in ≥10% of patients, n (%)</b>				
Infections and infestations	25 (61.0)	48 (56.5)	8 (72.7)	13 (81.3)
Otitis media	15 (36.6)	27 (31.8)	5 (45.5)	7 (43.8)
Sinusitis	8 (19.5)	11 (12.9)	2 (18.2)	2 (12.5)
Pneumonia	6 (14.6)	10 (11.8)	2 (18.2)	2 (12.5)
Conjunctivitis	5 (12.2)	9 (10.6)	0	1 (6.3)
Upper respiratory tract infection	7 (17.1)	9 (10.6)	0	3 (18.8)
Eye infection	2 (4.9)	3 (3.5)	1 (9.1)	2 (12.5)
Gastrointestinal disorders	16 (39.0)	24 (28.2)	1 (9.1)	2 (12.5)
Diarrhoea	8 (19.5)	12 (14.1)	1 (9.1)	2 (12.5)
Vomiting	6 (14.6)	9 (10.6)	0	0
Respiratory, thoracic, mediastinal disorders	13 (31.7)	23 (27.1)	3 (27.3)	4 (25.0)
Cough	7 (17.1)	13 (15.3)	0	0
Rhinitis allergic	6 (14.6)	9 (10.6)	0	0
Nasal congestion	0	0	1 (9.1)	2 (12.5)
Investigations	8 (19.5)	15 (17.6)	3 (27.3)	5 (31.3)
ALT increased	5 (12.2)	8 (9.4)	0	0
Neutrophil count decreased	4 (9.8)	8 (9.4)	1 (9.1)	2 (12.5)
General disorders, administration site	9 (22.0)	12 (14.1)	4 (36.4)	4 (25.0)
Pyrexia	6 (14.6)	9 (10.6)	4 (36.4)	4 (25.0)
Musculoskeletal, connective tissue disorders	4 (9.8)	5 (5.9)	1 (9.1)	3 (18.8)
Pain in extremity	3 (7.3)	4 (4.7)	1 (9.1)	3 (18.8)

Source: Tables 2.34 and 2.38, p126 and p131 of the submission.

AE=adverse event; ALT=alanine aminotransferase; n = number of participants reporting data; N = total participants in group; SAE=serious adverse event

6.28 A total of 77 patients (76.2%) reported an AE and the majority of AEs were Grade 2 or 3. Few patients experienced a serious adverse event (SAE) (10.9%), AEs leading to dose modification (6.9%) or AEs leading to dose interruption / discontinuation (10.9%). No deaths occurred as a result of a reported AE. The most commonly reported AEs were otitis media, sinusitis, pneumonia, upper respiratory tract infection, conjunctivitis, diarrhoea, vomiting, cough, allergic rhinitis, pyrexia, decreased neutrophils and increased alanine aminotransferase (ALT). Changes in hearing ability were also observed during Study 3b, but the incidence was low and events generally resolved with dose modification and/or temporary interruption.

### **Study 3b and Study 14**

6.29 Based on a pooled safety population from Study 3b and Study 14 (which was excluded from the analyses in the submission, paragraph 6.12), the FDA recommended the addition of warnings for monitoring for myelosuppression, hepatotoxicity and hearing loss to the label (Section 11, p366 CDER 2021<sup>15</sup>). These have been included in the draft PI. The FDA determined that spontaneous post-marketing AE reporting would not be adequate, and required the Sponsor to (i) conduct an integrated safety analysis of clinical trial data to assess and characterise the risk factors and sequelae of severe adverse reactions, with a final report due December 2027; and (ii) conduct a clinical pharmacokinetic trial to determine an appropriate dose of eflornithine to minimise the potential risks of increased drug toxicity in patients with renal impairment, with the final report due March 2026 (FDA 2023<sup>16</sup>).

### **Benefits/harms**

#### **STRATUM 1 AND STRATUM 2 PATIENTS**

##### **Study 3b: Eflornithine + SOC versus SOC (via unadjusted comparison to historical controls)**

6.30 The design of Study 3b did not allow for a quantitative comparison of the benefits and harms of eflornithine plus SOC versus SOC. Accordingly, a benefits/harms table has not been presented.

#### **STRATUM 1 PATIENTS**

##### **PSM study: Eflornithine + SOC versus SOC (via adjusted comparison to historical controls)**

6.31 Based on the available results from the PSM study, for every 100 patients in remission after upfront therapy (Stratum 1) and treated with eflornithine (for a period of up to 2 years) in comparison to SOC:

- Approximately 12 more patients would remain event free (i.e. in remission) after 4 years;
- Approximately 11 more patients would remain alive after 4 years.

### **Clinical claim**

6.32 The submission described eflornithine as superior in terms of effectiveness compared with SOC and inferior but manageable in terms of safety compared to SOC for both Stratum 1 and Stratum 2 patients.

6.33 The evaluation and the ESC considered that the clinical claim of superior effectiveness was likely reasonable given the available evidence. While the ESC noted that the

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<sup>15</sup> Center for Drug Evaluation and Research. 2021. Multi-Discipline Review. Application number: 21550Orig1s000. July 2021. Available at: [Review](#)

<sup>16</sup> FDA. NDA Approval Letter. NDA 215500. December 2023. Available at: [Approval Letter 215500Orig1s000ltr.pdf](#)

magnitude of the benefit was uncertain and the level of evidence varied by patient strata, it acknowledged the difficulty of obtaining high quality clinical evidence in this patient group.

- For Stratum 1 patients (those in remission at the end of upfront therapy), the results for Study 3b showed that patients treated with eflornithine had improved EFS and OS event rates at 24- and 48-months compared to unadjusted historical control data from Study ANBL0032. The ESC noted that these findings were supported by the PSM study, which had well-matched patients in Study 3b and Study ANBL0032 based on covariates from a similar index date. Although the HRs suggested a large treatment effect (for the PSM study, EFS HR 0.49 [95%CI: 0.28, 0.86], and OS HR 0.33 [95%CI: 0.16, 0.70]), the confidence intervals were relatively wide and moderately sensitive to the study assumptions. The potential impact of residual confounding further adds some degree of uncertainty around magnitude of treatment effects.
- For Stratum 2 patients (those in remission after any previous therapy for relapsed or refractory disease), the results for Study 3b showed that patients treated with eflornithine had improved EFS event rates at 24- and 48-months compared to unadjusted historical control data from Santana 2008 (OS data was not presented). Although the results were promising given the poor prognosis of relapsed/refractory patients and implied a very large incremental treatment effect, the ESC noted that the unadjusted comparison had a high risk of bias for a number of reasons (e.g. small sample size, lack of contemporary comparator, differences in outcome definition and index date, no assessment of differences in confounders).

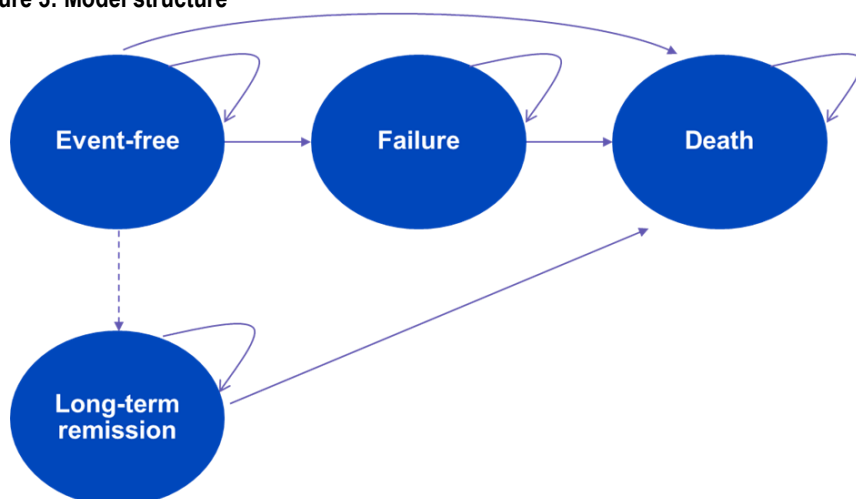
6.34 The PBAC considered that the claim of superior comparative effectiveness over SOC was reasonable for Stratum 1 patients, based on the Study 3b and PSM results for EFS and OS, but uncertain for Stratum 2 patients, due to the unmatched clinical comparison with a high risk of bias.

6.35 The ESC agreed with the evaluation that the clinical claim of inferior safety was appropriate, noting the FDA warnings for hepatotoxicity, myelosuppression, and hearing loss. The PBAC agreed with the ESC that the clinical claim of inferior safety was appropriate, and noted the registration requirements with respect to safety set out in the TGA Delegate's Overview (paragraph 2.2).

### ***Economic analysis***

6.36 The submission presented a cost-utility analysis (CUA) using a partitioned survival analysis model with four health states: event free (EF) disease, relapse, long-term remission (LT-remission), and death. The submission modelled the Stratum 1 and Stratum 2 populations separately using the same model structure but different parameters. The model diagram is presented in Figure 3.

Figure 3: Model structure



Source: Figure 3-1 of the submission

6.37 Key components of the economic evaluation are presented in Table 7. The submission did not present a stepped analysis.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Eflornithine vs SOC (no active treatment)
Time horizon	100 years in the model base case vs. median OS follow up 7.21 years in Study 3b Stratum 1 (Stratum 2 not reported) and 5.85 years in Study ANBL0032. The evaluation noted that while a lifetime model may be reasonable, the extrapolation to 100 years was uncertain compared to the length of the study data.
Outcomes	LYs and QALYs gained using separate models for Stratum 1 and Stratum 2 populations.
Methods used to generate results	Partitioned survival model, which the evaluation considered to be reasonable, although the resulting proportion allocated to relapse in Stratum 1 was small (health state allocation to relapse was <15% across the time horizon) and the approach could not track individual patients, which had implications for the cost of subsequent treatment (see table row below – Subsequent therapy costs)
Health states	EF, LT-remission, relapse, dead. The evaluation considered that these health states were reasonable, though patients in Stratum 1 who relapsed could not return to event free or achieve long-term remission, which is inconsistent with the assumption that the Stratum 2 population exists.
Cycle length	4 weeks (no half-cycle correction). The evaluation considered that this was reasonable, although the model assumed 52 weeks per year, and therefore, there were some slight rounding errors. Furthermore, eflornithine costs were applied at the end of the first model cycle and <100% of patients in the eflornithine arm received eflornithine (0.4% did not) [this error would be exacerbated by a longer cycle length].
Allocation to health states	Stratum 1: PSM analysis of Study 3b Stratum 1 and Study ANBL0032 to Yr 7. Stratum 2: Study 3b Stratum 2 and PSM analysis Study 3b Stratum 1 populations to Yr 7. Standardised mortality ratio applied to general population from Yr 7 in both models.
Extrapolation method	<b>EFS: Stratum 1:</b> Independent Gompertz extrapolations of PSM matched Study 3b Stratum 1 and ANBL0032 data from Time 0 to Yr 7 (“cure” time point). <b>Stratum 2:</b> Stratum 1 extrapolation with HR 5.13 applied from Time 0 to Yr 7. <b>OS: Stratum 1:</b> Independent generalised gamma extrapolations of PSM matched Study 3b Stratum 1 and ANBL0032 data from Time 0 to Yr 7. <b>Stratum 2:</b> Stratum 1 extrapolation with HR 7.96 applied from Time 0 to Yr 7. <b>LT-remission:</b> 100% patients alive and EF from Yr 7 in <b>both populations</b> . Death from LT-remission was estimated with a standardised mortality ratio applied to general population mortality. Without a cure point, the models still intrinsically modelled patients as cured as Gompertz EFS extrapolations resulted in long, level tails.

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Component	Summary
	<p><b>Relapse:</b> the difference between OS and EFS. Patients could not move to relapse after Year 7. Death from relapse was equal to extrapolated OS from Yr 7.</p> <p><b>TTD</b> PSM analysis of Study 3b Stratum 1 KM data.</p> <p>The Stratum 2 transition probabilities were highly uncertain and were highly dependent on the relationship between Stratum 1 and Stratum 2 from Study 3b being applicable to the Australian population.</p>
Health related quality of life	<p>Paediatric population norms based on EQ-5D-5L adult population norms (McCaffrey 2016) with utility decrements: 7.3% for EF and LT remission states, 41.7% relapse state based on HUI2 and HUI3 values from Portwine 2016 and Barr 1999. The same approach as the dinutuximab beta MSAC model was used (Table 10, dinutuximab beta Public Summary Document (PSD), July 2020 MSAC meeting), assuming that utilities derived from HUI2, HUI3 and EQ-5D-5L were directly transferrable, which the evaluation noted was not methodologically appropriate. It may also not be reasonable to assume an ongoing decrement over the lifetime for “cured” patients (Kwon 2018).</p> <p>Further utility decrements were applied in Cycle 1 for patients receiving eflornithine based on AEs of anaemia, decreased neutrophil count, hearing loss and diarrhoea. The total QALY loss associate with eflornithine treatment was -0.022 QALYs per person and therefore the ICER was not sensitive to AEs.</p>
Eflornithine costs	<p>The cost of eflornithine was based on the proposed EMP of \$ [REDACTED] for 100x250mg tablets (\$ [REDACTED] per tablet), and the corresponding cost of eflornithine treatment per 28-day cycle was estimated as \$ [REDACTED] per cycle in Yr 1 and \$ [REDACTED] per cycle in Yr 2. The evaluation noted that there were several concerns with the cost of eflornithine applied in the model:</p> <ul style="list-style-type: none"> <li>• use of EMP rather than DPMQ;</li> <li>• &lt;100% of patients received cost of eflornithine in the first model cycle;</li> <li>• eflornithine could continue in relapse and this cost was double-counted;</li> <li>• pack wastage at the cohort level, which the evaluation considered to be uncertain;</li> <li>• no dosing was directly from Study 3b, instead estimating dose based on projected BSA (estimated from patient age and sex) and then adjusting with a dose modifier (103.6%), which the evaluation could not verify. Dose was not altered by changing age at baseline in the model.</li> </ul>
Subsequent therapy costs	<p>One-off cost (\$213,381) for a year of subsequent therapy (dinutuximab plus irinotecan and temozolomide, plus additional MIBG, CT and MRI costs) was applied to the proportion of patients relapsing each cycle. As the model was memoryless (i.e., did not follow individual patients), subsequent therapy costs were only applied if the proportion in relapse in each cycle had increased from the previous cycle. Therefore, when mortality was equal to or exceeded the probability of relapse, the cost of relapse was not applied, and the proportion of patients receiving subsequent therapy was likely underestimated.</p>

Source: compiled during the evaluation using Table 3-1, pp143-144, Section 3.2.4 p 152, Sections 3.4.2.1-3.4.2.2, pp157-172, Table 3-16, p180, Section 3.6.1.1 pp181-184 Table 3-25, p187 of the submission

AEs = adverse events, BSA=body surface area, CT=computed tomography, DPMQ=dispensed price for maximum quantity, EF=event free, EFS=event free survival, EMP=ex-manufacturer price, EQ-5D-5L=EuroQoL-5 dimensions-5 levels, HR=hazard ratio, HUI=health utilities index, ICER = incremental cost effectiveness ratio, KM=Kaplan-Meier, LT=long-term, LY=life year, MIBG=meta-iodobenzylguanidine, MRI=magnetic resonance imaging, OS=overall survival, PSD=Public Summary Document, PSM=propensity score matching, QALY=quality adjusted life year, SOC=standard of care.

6.38 EFS and OS extrapolations for the Stratum 1 population were fitted on all KM data available from the PSM analysis of Study 3b Stratum 1 and Study ANBL0032 (8.5 years in the eflornithine arm, 11.6 years in the SOC arm). A high proportion of patients were censored compared to those who experienced an event by Year 6, with less than 20% of each arm remaining at risk by Year 8 for both EFS and OS. As such, small numbers of patients shaped the long-term extrapolations. Based on visual and statistical fit, as well as clinical plausibility for the shape of the hazard over time, the submission chose Gompertz extrapolations for EFS and generalised gamma for OS in both arms of the Stratum 1 model. The evaluation noted the chosen extrapolations produced the

longest tails for EFS and OS. The PSCR stated that curve selection was based on standard criteria (AIC, BIC<sup>17</sup> and visual fit). Additionally, the alternative distributions appear to overfit to the lower portion of the data, whilst the Gompertz [for EFS] was matched across the entirety of the data. The PSCR stated that while a long tail is consistently observed in HRNB studies, it was acknowledged that any curve that demonstrates zero risk is implausible and this was addressed by application of a cure point (see paragraph 6.41 below), after which time general population mortality was applied.

- 6.39 For the Stratum 2 population, the submission applied an EFS hazard ratio of 5.13 (95%CI 2.56, 10.28) and OS hazard ratio 7.96 (95%CI 3.26, 19.43) to the Stratum 1 base case extrapolations of both arms. The hazard ratios were derived from the comparison of the Study 3b Stratum 2 population versus the Study 3b Stratum 1 PSM population.<sup>18</sup> The evaluation noted that this approach may overestimate the effect of eflornithine as it predicts a larger difference between the eflornithine and SOC arms in Stratum 2 than estimated in the PSM study for Stratum 1.
- 6.40 As the base case EFS extrapolations would eventually exceed OS extrapolations in all arms of both models, EFS curves were capped to not exceed OS. The submission assumed a cure point in both the Stratum 1 and 2 populations at Year 7, and all patients in EFS at Year 7 transitioned to LT-remission. Without a set cure point, the extrapolations mimicked a cure point, with the EFS extrapolations all plateauing around Year 5, resulting in very few patients transitioning out of the EF health state before dying beyond Year 5. As such, the cure point only affected long term survival, rather than relapse rates.
- 6.41 After the assumed cure point at Year 7, the OS extrapolations continued to be applied to relapsed patients, which the evaluation considered may not be reasonable as they were estimated from both EF and relapsed patients and resulted in a survival benefit for relapsed patients in the eflornithine arm over the SOC arm. Mortality from LT-remission was estimated by applying a standardised mortality ratio (SMR) of 5.6 from Laverdière 2009 to age-based general population mortality (ABS life tables). This approach to mortality in LT-remission appeared similar to that previously applied in the dinutuximab submission to MSAC (Table 10, dinutuximab beta Public Summary Document [PSD], July 2020 MSAC meeting), except applied to an earlier time point (Year 7 compared to Year 10 in the dinutuximab beta model).
- 6.42 Time to treatment discontinuation (TTD) of eflornithine was modelled based on the KM data for Stratum 1 in Study 3b, capped to not exceed mortality or 2 years maximum treatment. Time on treatment was incorrectly applied to the modelled costs, with patients on treatment in relapse double-counted each cycle. Time on treatment was corrected during the evaluation, altering the base case incremental

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<sup>17</sup> AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion

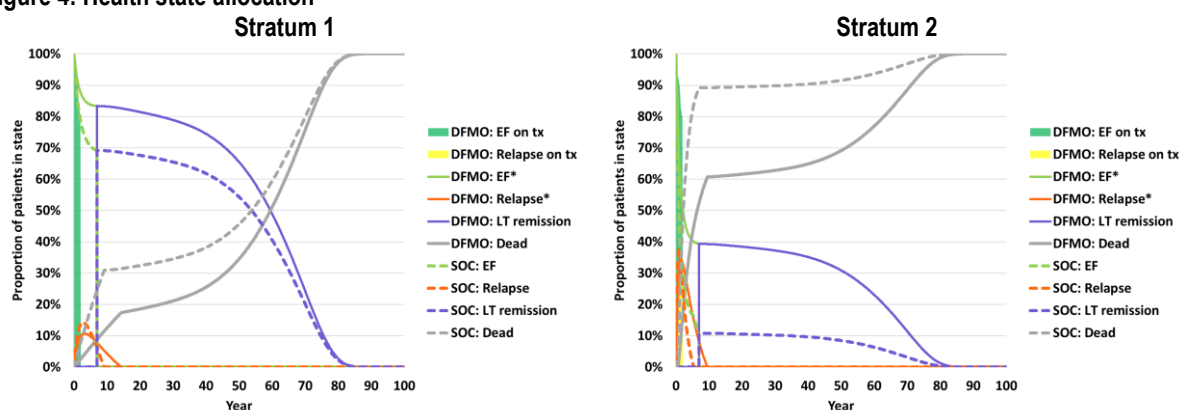
<sup>18</sup> In this analysis, one patient from Stratum 1 was excluded as they were included in the Stratum 2 population.

cost effectiveness ratios (ICERs) from \$155,000 to < \$255,000 per QALY gained for Stratum 1 and \$95,000 to < \$115,000 per QALY gained for Stratum 2 to \$155,000 to < \$255,000 and \$75,000 to < \$95,000 per QALY gained, respectively.

- 6.43 No quality of life data was available from Study 3b; instead, the submission implemented an approach similar to that for presented for dinutuximab beta (Table 10, dinutuximab beta PSD, July 2020 MSAC meeting). The submission estimated age-based utility weights for patients in the EF, LT-remission and relapse health states from EQ-5D-5L adult population norms (McCaffrey 2016) with utility decrements: 7.3% for EF and LT remission states, and 41.7% relapse state based on HUI2 and HUI3 values from Portwine 2016 and Barr 1999. The submission assumed that utilities derived from HUI2, HUI3 and EQ-5D-5L were directly transferrable, which the evaluation considered was not methodologically appropriate, noting that the ICERs were sensitive to the underlying general population and EF/LT-remission utility estimates. The PSCR stated that in the absence of trial-based utility values from Study 3b, literature-based values were used that have been considered appropriate for decision-making in the United Kingdom and Australia. Further, the PSCR referred to the challenge of measuring QoL for very rare diseases in an orphan, paediatric population such as HRNB.
- 6.44 The cost of eflornithine was based on an ex-manufacturer price (EMP) of \$ [REDACTED] for 100x250 mg tablets (\$ [REDACTED] per tablet). The submission assumed patients would receive a weighted average of 4.7 tablets per day in Year 1 and a weighted average of 5.2 tablets per day in Year 2 based on projected BSA distribution in Study 3b Stratum 1, according to the individual age and sex of the patients in Study 3b Stratum 1. With a dosing adjustment of 103.6% based on the comparison of actual treatment versus predicted treatment received for the Study 3b Stratum 1 safety set (n=85), the corresponding cost of eflornithine treatment was \$ [REDACTED] per 28-day cycle in Year 1 and \$ [REDACTED] per 28-day cycle in Year 2. Pack wastage was also applied, where the number of tablets required for the cohort was rounded to the nearest 100 each cycle. Per cycle cost was applied to the proportion of patients estimated to be on treatment in the EF and relapse states.
- 6.45 There were several concerns with the cost of eflornithine applied in the model in addition to the double-counting of patients receiving eflornithine in relapse, such as:
- utilising EMP rather than the dispensed price for maximum quantities (DPMQs);
  - not costing eflornithine for 0.4% patients in the first model cycle;
  - the dose modifier not being verifiable;
  - age at baseline not affecting the dose estimates.
- 6.46 The EF and relapse health states accrued costs per cycle for meta-iodobenzylguanidine (MIBG), CT scan, MRI, blood, urine, bone marrow testing and abdominal ultrasound. THE frequency was based on expert opinion from 10 paediatric oncologists (6 specialising in HRNB).

- 6.47 A one-off cost (\$213,381) for a year of subsequent therapy (dinutuximab plus irinotecan and temozolomide plus additional MIBG, CT and MRI costs for diagnosing relapse, based on clinical opinion) was applied to the proportion of patients relapsing each cycle. There are currently no specific guidelines for treatment in relapse and not all patients who experience relapse will receive a full year of treatment (particularly Stratum 2 patients who have a longer history of prior treatment than Stratum 1 patients); therefore, the evaluation considered that this one-off cost may be overestimated. Removing the cost of subsequent therapy increased the Stratum 1 ICER by 1%.
- 6.48 Cohort traces are presented in Figure 4. For the majority of the time horizon, Stratum 1 patients were either in EF, LT-remission or dead state, with a low percentage of patients who ever entered the relapse health state, which was consistent with the choice of EFS extrapolation and assumption that patients who achieve long term EFS will not experience disease progression beyond Year 7. In both models, the absolute incremental difference in health state occupancy of the relapse state was small, though the relative incremental difference was larger, given the improved survival in the eflornithine arms. At the end of the time horizon 0% patients remained alive in either arm of both models.

Figure 4: Health state allocation



Source: compiled during the evaluation using Sheets 'DFMO Trace' and 'WW Trace' of Excel workbook 'EFLORNITHINE – Cost effectiveness analysis. Final model 4thNov\_2024 PBAC submission.xlsx'

DFMO= difluoromethylornithine = eflornithine arm, EF=event free, LT=long-term, SOC=standard of care arm, tx=treatment

\* EF and Relapse curves in the eflornithine arm include patients on and off treatment

6.49 A summary of the key drivers of the model is presented in Table 8.

Table 8: Key drivers of the model

Description	Method/Value	Impact Corrected base case: Stratum 1 \$ [redacted] /QALY gained Stratum 2 \$ [redacted] /QALY gained.
Treatment effect size (to Year 7)	<p>Stratum 1 EFS and OS benefit for eflornithine to Year 7 was based on extrapolated KM data from the PSM analysis of Study 3b Stratum 1 and Study ANBL0032. This was also carried through to the Stratum 2 analysis. This submission did not address the uncertainty in these estimates, e.g., the EFS HR from the PSM analysis had EFS HR 95%CI 0.282, 0.855 and OS HR 95%CI 0.158, 0.703</p> <p>Stratum 2 EFS and OS benefit for eflornithine to Year 7 was further based on the point estimate HRs between Study 3b Stratum 2 and PSM analysis of Study 3b Stratum 1 KM data. The submission did not address the uncertainty in these point estimates, EFS HR 95%CI 2.56, 10.28 and OS HR 95%CI 3.26, 19.43; and did not provide evidence to validate the Stratum 2 model SOC arm, resulting in further uncertainty.</p>	<p>High, uncertain impact. If the PSM HRs were applied, the ICERs ranged from \$ [redacted]<sup>3</sup> to \$ [redacted]<sup>4</sup>/QALY gained for Stratum 1, \$ [redacted]<sup>3</sup> to \$ [redacted]<sup>5</sup>/QALY gained for Stratum 2.</p> <p>For Stratum 2 if the Stratum 2 vs Stratum 1 EFS HR 95%CI was explored, the ICER ranged from \$ [redacted]<sup>3</sup> to \$ [redacted]<sup>6</sup>/QALY gained. Similarly, if the OS HR 95%CI was explored, the ICER ranged from \$ [redacted]<sup>2</sup> to \$ [redacted]<sup>6</sup>/QALY gained</p>
Cure threshold	<p>The submission assumed patients alive and event free at Year 7 would enter LT-remission and would not experience relapse beyond this point (i.e., assumed “cured”). A cure point is likely reasonable, particularly for Stratum 1 patients. However, the extrapolations of EFS in the base case effectively mimicked a cure point, with the EFS extrapolations all plateauing around Year 5, resulting in very few patients transitioning out of the EF health state before dying beyond Year 5. As such, the cure point only affected long term survival, rather than relapse rates.</p> <p>The evaluation considered that the timing of the cure threshold was not well justified; in the dinutuximab beta MSAC submission the threshold was 10 years.</p>	<p>High, favoured SOC in Stratum 1 model, favoured eflornithine in Stratum 2 model. Without the cure point the Stratum 1, the ICER decreased to \$ [redacted]<sup>7</sup>/QALY gained, and the Stratum 2 ICER increased to \$ [redacted]<sup>7</sup>/QALY gained. However, the inclusion of a cure point was likely to be more reasonable.</p>
Time horizon	<p>100 years in the base case, versus median OS follow up 7.21 years in Study 3b Stratum 1 (Stratum 2 not reported), and 5.85 years in Study ANBL0032</p>	<p>High, favoured eflornithine. If time horizon reduced to 25 years (patients follow to ~age 30), the ICERs increased to \$ [redacted]<sup>1</sup>/QALY gained and \$ [redacted]<sup>8</sup>/QALY gained in Stratum 1 and Stratum 2 populations respectively.</p>
Utility	<p>Paediatric population norms based on EQ-5D-5L adult population norms (McCaffrey 2016) with utility decrements: 7.3% for EF and LT remission states, 41.7% relapse state based on HUI2 and HUI3 values from Portwine 2016 and Barr 1999.</p>	<p>High, favoured eflornithine. In one-way sensitivity analyses if utility was reduced in the EF/LT-remission states by 20%, the Stratum 1 ICER increased to \$ [redacted]<sup>1</sup>/QALY gained and the Stratum 2 ICER to \$ [redacted]<sup>7</sup> per QALY gained.</p>
Time on treatment	<p>Study 3b Stratum 1 TTD KM data capped at 2 years in line with requested restriction. Patients could receive eflornithine in relapse when TTD exceed EFS extrapolation (particularly significant in the Stratum 2 population). As eflornithine may be seen as a less toxic therapy than other treatments in this area, patient families may wish to extend time on treatment while a benefit is observed.</p>	<p>High, favoured eflornithine. If eflornithine treatment was extended to all patients in the EF health state but no patients in relapse or LT-remission, the ICERs increased to \$ [redacted]<sup>9</sup>/QALY gained for Stratum 1 and \$ [redacted]<sup>6</sup>/QALY gained for Stratum 2</p>

Description	Method/Value	Impact Corrected base case: Stratum 1 \$ [redacted] /QALY gained Stratum 2 \$ [redacted] /QALY gained.
Subsequent therapy cost	One-off cost (\$213,380.76) for a year of subsequent therapy was applied to the proportion of patients relapsing each cycle. Due to the memoryless and cohort nature of the model, the submission estimated the number of patients receiving subsequent therapy each cycle only when the proportion of patients in relapse increased from the cycle before and generally lacks face validity.	High, favoured SOC in the Stratum 2 model. Removing the relapse costs decreased the Stratum 2 ICER to \$ [redacted] /QALY gained and increased the Stratum 1 ICER to \$ [redacted] /QALY. It was not possible to fully explore the uncertainty in incident relapse each cycle.

Source: compiled during the evaluation.

EF=event free, EFS=event free survival, EQ-5D-5L=EuroQoL-5 dimensions-5 levels, HR=hazard ratio, HUI=health utilities index, ICER=incremental cost-effectiveness ratio, KM=Kaplan-Meier, LT=long-term, MSAC=Medical Services Advisory Committee, PSM=propensity score matched, QALY=quality adjusted life year, SOC=standard of care, TTD=time to treatment discontinuation.

The redacted values correspond to the following ranges:

<sup>1</sup>\$155,000 to < \$255,000

<sup>2</sup>\$75,000 to < \$95,000

<sup>3</sup>\$55,000 to < \$75,000

<sup>4</sup>\$655,000 to < \$755,000

<sup>5</sup>\$355,000 to < \$455,000

<sup>6</sup>\$135,000 to < \$155,000

<sup>7</sup>\$95,000 to < \$115,000

<sup>8</sup>\$115,000 to < \$135,000

<sup>9</sup>\$455,000 to < \$555,000

6.50 The ESC agreed with the evaluation that issues in the economics were largely driven by uncertainty in the available eflornithine clinical data, particularly in Stratum 2, and reliance on PSM analysis with small patient numbers. The ESC particularly noted the key model drivers of length of benefit, assumption of cure point, utility in EF and LT-remission health states, cost of eflornithine with respect to time on treatment, and cost of relapse.

6.51 Table 9 presents the results of the economic evaluation. The submitted base case ICER for Stratum 1 was \$155,000 to < \$255,000 per QALY gained and for Stratum 2 was \$95,000 to < \$115,000 per QALY gained. Once time on eflornithine was corrected, the ICERs were \$155,000 to < \$255,000 and \$75,000 to < \$95,000 per QALY gained in the Stratum 1 and Stratum 2 models, respectively. Throughout the results and sensitivity analyses, the corrected base case is utilised.

Table 9: Results of the economic evaluation

Component	Stratum 1			Stratum 2		
	Eflornithine	SOC	Increment	Eflornithine	SOC	Increment
Costs (submission)	\$ [redacted]	\$31,169	\$ [redacted]	\$ [redacted]	\$80,518	\$ [redacted]
Costs (corrected)	\$ [redacted]	\$31,169	\$ [redacted]	\$ [redacted]	\$80,518	\$ [redacted]
LYs	16.92	14.25	2.67	9.50	3.97	5.52
QALYs	14.56	12.31	2.25	7.90	3.24	4.66
Incremental cost/extra LY gained (submission)			\$ <sup>4</sup> [redacted]			\$ <sup>3</sup> [redacted]
Incremental cost/extra LY gained (corrected)			\$ <sup>4</sup> [redacted]			\$ <sup>3</sup> [redacted]
<b>Incremental cost/extra QALY gained (submission)</b>			\$ <sup>1</sup> [redacted]			\$ <sup>2</sup> [redacted]
<b>Incremental cost/extra QALY gained (corrected)</b>			\$ <sup>1</sup> [redacted]			\$ <sup>3</sup> [redacted]

Source: Tables 3-30, 3-31, 3-47, 3-48 of the submission and compiled during the evaluation

SOC=standard of care, LY=life year, QALY=quality adjusted life year

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The redacted values correspond to the following ranges:

<sup>1</sup>\$155,000 to < \$255,000

<sup>2</sup>\$95,000 to < \$115,000

<sup>3</sup>\$75,000 to < \$95,000

<sup>4</sup>\$115,000 to < \$135,000

6.52 The model estimated an increase in cured patients of 14.2% in Stratum 1 (83.4% event free at Year 7 in the eflornithine arm compared to 69.2% in the SOC arm) and 28.5% in Stratum 2 (39.3% event free at Year 7 in the eflornithine arm compared to 10.8% in the SOC arm). Overall, this resulted in the submission assuming that for every event free life year gained (up to Year 7) in the eflornithine arm versus SOC, patients in Stratum 1 would gain 12.7 additional life years over their lifetime, and patients in Stratum 2 would gain 11.3 additional life years over their lifetime.

6.53 The cost of eflornithine was the largest contributor to incremental undiscounted cost (\$, % of the incremental cost in the Stratum1 model, % of the incremental cost in the Stratum 2 model). The cost of subsequent therapy was the largest cost offset in the Stratum 1 model (-\$, -% of the incremental cost) and the second largest contributor to incremental undiscounted cost in the Stratum 2 population (\$, % incremental cost). More patients were predicted to experience relapse in the eflornithine arm of the Stratum 2 model than the SOC arm as a result of improved survival.

6.54 The results of key sensitivity analyses are summarised in Table 10. The ICERs were sensitive to inputs that affected EFS and OS benefit (including length of benefit and timing of cure point), utility in EF/LT-remission states, cost of eflornithine and cost of relapse. The sensitivity analyses could not address all the uncertainty arising from the PSM, the downstream assumptions, and the overall uncertainty in modelling based on small numbers of patients (particularly Stratum 2).

Table 10: Sensitivity analyses

Analyses	Stratum 1				Stratum 2			
	Incr. cost	Incr. QALY	ICER	% change	Incr. cost	Incr. QALY	ICER	% change
<b>Corrected base case</b>	\$█	2.25	\$█ <sup>1</sup>	-	\$█	4.66	\$█ <sup>2</sup>	-
Discount rate (base case 5% costs and outcomes)								
• 0%	\$█	7.58	\$█ <sup>3</sup>	█%	\$█	14.65	\$█ <sup>4</sup>	█%
• 3.5%	\$█	3.01	\$█ <sup>5</sup>	█%	\$█	6.09	\$█ <sup>6</sup>	█%
Time horizon (base case 100 years)								
• 25 years	\$█	1.65	\$█ <sup>1</sup>	█%	\$█	3.55	\$█ <sup>5</sup>	█%
• 50 years	\$█	2.16	\$█ <sup>1</sup>	█%	\$█	4.49	\$█ <sup>7</sup>	█%
EFS and OS extrapolation								
Stratum 1 EFS and OS extrapolation scenarios (base case: EFS Gompertz, OS gen. gamma from Time 0)								
• EFS log-normal	\$█	2.50	\$█ <sup>8</sup>	█%	-	-	-	-
• BICR assessment	\$█	1.83	\$█ <sup>1</sup>	█%	-	-	-	-
Stratum 1 PSM HR approach (base independent extrapolation, eflornithine extrapolations EFS Gompertz, OS generalised gamma). Stratum 2 approach as base case (Stratum 2 versus Stratum 1 HRs applied to Stratum 1 modelled arms)								
• EFS HR 0.49 (point est.)	\$█	2.29	\$█ <sup>3</sup>	█%	\$█	4.70	\$█ <sup>2</sup>	█%
• EFS HR 0.28 (lower CI)	\$█	3.84	\$█ <sup>2</sup>	█%	\$█	5.73	\$█ <sup>6</sup>	█%
• EFS HR 0.86 (upper CI)	\$█	1.41	\$█ <sup>9</sup>	█%	\$█	4.49	\$█ <sup>7</sup>	█%
• OS HR 0.33 (point est.)	\$█	2.24	\$█ <sup>1</sup>	█%	\$█	4.61	\$█ <sup>2</sup>	█%
• OS HR 0.16 (lower CI)	\$█	4.17	\$█ <sup>2</sup>	█%	\$█	6.37	\$█ <sup>6</sup>	█%

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Analyses	Stratum 1				Stratum 2			
	Incr. cost	Incr. QALY	ICER	% change	Incr. cost	Incr. QALY	ICER	% change
<b>Corrected base case</b>	\$█	2.25	\$█ <sup>1</sup>	-	\$█	4.66	\$█ <sup>2</sup>	-
• OS HR 0.70 (upper CI)	\$█	1.26	\$█ <sup>9</sup>	█%	\$█	3.20	\$█ <sup>5</sup>	█%
Stratum 2 EFS HR vs Stratum 1 (base case 5.13)								
• 2.56	-	-	-	-	\$█	5.69	\$█ <sup>6</sup>	-█%
• 10.28	-	-	-	-	\$█	3.51	\$█ <sup>8</sup>	█%
Stratum 2 OS HR vs Stratum 1 (base case 7.96)								
• 3.26	-	-	-	-	\$█	4.76	\$█ <sup>2</sup>	-█%
• 19.43	-	-	-	-	\$█	3.17	\$█ <sup>8</sup>	█%
Relapse mortality SMR 10.6 (base case uses trial)	\$█	2.15	\$█ <sup>1</sup>	█%	\$█	5.20	\$█ <sup>2</sup>	-█%
Cure time point (base case 7 years)								
• 10 years	\$█	2.30	\$█ <sup>3</sup>	-█%	\$█	5.12	\$█ <sup>2</sup>	-█%
• None	\$█	3.17	\$█ <sup>7</sup>	-█%	\$█	4.14	\$█ <sup>5</sup>	█%
TTD (base case KM data to 2 year cap)								
• Remove cap	\$█	2.25	\$█ <sup>1</sup>	█%	\$█	4.66	\$█ <sup>7</sup>	█%
• Equal to EF, 2 year cap	\$█	2.25	\$█ <sup>1</sup>	█%	\$█	4.66	\$█ <sup>6</sup>	-█%
• Equal to EF, cap at cure point (7 year)	\$█	2.25	\$█ <sup>10</sup>	█%	\$█	4.66	\$█ <sup>8</sup>	█%
Utilities (base age based with -7.3% decrement in EF/LT-remission, -41.7% in relapse)								
• EF/LT-remission +20%	\$█	2.68	\$█ <sup>5</sup>	-█%	\$█	5.54	\$█ <sup>2</sup>	-█%
• EF/LT-remission -20%	\$█	1.82	\$█ <sup>1</sup>	█%	\$█	3.78	\$█ <sup>7</sup>	█%
No costs in relapse (base one-off, plus per cycle costs)	\$█	2.25	\$█ <sup>1</sup>	█%	\$█	4.66	\$█ <sup>2</sup>	-█%
<b>Multivariate analyses</b>								
Stratum 1 modelling approach (Stratum 2 equal to Stratum 2 versus Stratum 1 HRs applied to Stratum 1 modelled arms)								
• EFS HR=0.49 and OS HR=0.33 (point estimates)	\$█	2.28	\$█ <sup>3</sup>	-█%	\$█	4.65	\$█ <sup>2</sup>	-█%
• EFS HR=0.28 and OS HR=0.16 (lower 95% CI)	\$█	4.83	\$█ <sup>6</sup>	-█%	\$█	6.55	\$█ <sup>6</sup>	-█%
• EFS HR=0.86 and OS HR=0.70 (upper 95% CI)	\$█	0.50	\$█ <sup>11</sup>	█%	\$█	1.01	\$█ <sup>12</sup>	█%

Source: compiled during the evaluation using scenarios in Sections 3.9.3 and 3.10.5.4 of the submission  
 CI=confidence interval; EF=event free, OS=overall survival, EFS=event free survival, HR=hazard ratio. TTD=time to treatment discontinuation, SMR=standardised mortality ratio, BICR=blinded independent central review conducted at an earlier database lock, LT=long term.

The redacted values correspond to the following ranges:

- <sup>1</sup>\$155,000 to < \$255,000
- <sup>2</sup>\$75,000 to < \$95,000
- <sup>3</sup>\$45,000 to < \$55,000
- <sup>4</sup>\$25,000 to < \$35,000
- <sup>5</sup>\$115,000 to < \$135,000
- <sup>6</sup>\$55,000 to < \$75,000
- <sup>7</sup>\$95,000 to < \$115,000
- <sup>8</sup>\$135,000 to < \$155,000
- <sup>9</sup>\$255,000 to < \$355,000
- <sup>10</sup>\$455,000 to < \$555,000
- <sup>11</sup>\$655,000 to < \$755,000
- <sup>12</sup>\$355,000 to < \$455,000

## Eflornithine cost/patient/course

Table 11: Drug cost per patient for proposed and comparator drugs

	Eflornithine Stratum 1			Eflornithine Stratum 2		
	Study 3b dose and duration ITT 105 pts Safety set 85 pts	Model	Financial estimates	Study 3b dose and duration ITT 35 pts Safety set 16 pts	Model	Financial estimates
Mean daily dose	ITT: NR Safety set: 1264.3mg <sup>a</sup>	1363.9 mg (with wastage) 1274.9 mg (no wastage)	1285.2mg	ITT: NR Safety set: 1289.5mg <sup>b</sup>	1351.4 mg (with wastage) 1274.9 mg (no wastage)	1285.2 mg
Mean duration (no. 28 day cycles)	ITT: NR Safety set: 24.0	22.4 <sup>c</sup> (1.72 yrs)	26.1 cycles (2.0 years)	ITT: NR Safety set: 19.9	22.4 <sup>c</sup> (1.72 yrs)	26.1 cycles (2.0 years)
Cost/patient/course	-	\$█ (with wastage) \$█ (no wastage) <sup>d</sup>	\$█ <sup>e</sup>	-	\$█ (with wastage) \$█ (no wastage) <sup>d</sup>	\$█ <sup>e</sup>

Source: compiled during the evaluation from Table 19, p80 of the Study 3b CSR and Excel workbooks 'EFLORNITHINE – Cost effectiveness analysis. Final model 4thNov\_2024 PBAC submission .xslm' and 'Eflornithine\_BIM Stratum 1 and 2 including grandfathered patients Nov\_2024.xlsx'

ITT=intention to treat; NR=not report, pts=patients, yrs=years

a Sum of mean morning dose (631.6 mg) and evening dose (632.7 mg)

b Sum of mean morning dose (644.3 mg) and evening dose (645.2 mg)

c corrected number of cycles. In the submission, Stratum 1 22.4 cycles (1.72 years) and Stratum 2 27.5 cycles (2.11 years)

d model costs incorrectly used EMP \$█ for 100 tablets, rather than DPMQ.

e financial estimates use corrected DPMQ \$█ for 100 tablets, no pack wastage assumed

6.55 The estimated undiscounted average cost per patient per course of eflornithine was \$█ in Stratum 1 and Stratum 2 (corrected for errors in the submission, see paragraph 6.56) for 1.72 years of treatment, including pack wastage. Without pack wastage the cost per course of eflornithine was \$█ in Stratum 1 and Stratum 2. The financial estimates assumed 2 years on treatment for all patients and implemented DPMQ rather than EMP; therefore, the cost per person was higher: \$█.

### Estimated PBS usage & financial implications

6.56 This submission was considered by DUSC.

6.57 Table 12 outlines the key inputs relied on for the financial estimates.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment from evaluation
Incident NBL patients	Yr 1: 81, Yr 2: 82, Yr 3: 83, Yr 4: 84, Yr 5: 85, Yr 6: 86 ABS population 0-21 years (2025-2030) and NBL incidence trend in children 0-14 years old from Youlden 2020 (submission stated 10.6 per million children, 9.5 per million children reported in Youlden 2020).	Likely overestimated because it may not be appropriate to apply the same rate based on ages 0-14 years to 15-21 years who have a much lower incidence. Further, the incidence of neuroblastoma was higher than expert opinion (40-50, ANZCHOG 2024 and clinical opinion) and previous estimates of 50-59 patients per year in Table 17 dinutuximab beta PSD July 2020 MSAC meeting.
% who meet Stratum 1 criteria	52.6% high-risk (Youlden 2020) x 79.8% respond to induction (Pinto 2019) x 92.2% respond to consolidation (Granger	The populations in these studies had some overlap but generally differed to each other and to Study 3b; therefore, these estimates are uncertain.

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Parameter	Value applied and source	Comment from evaluation
	2022) x 84.0% complete maintenance (Desai 2022) x 97.4% response after maintenance (Desai 2022)	
% who meet Stratum 2 criteria	<b>Refractory:</b> 52.6% high-risk (Youlden 2020) x 20.2% do not respond to induction (Pinto 2019) x 54.0% alive at 2.5 yrs (Pinto 2019) x 34.0% respond to immunotherapy (CADTH 2021) <b>Relapsed:</b> 52.6% high-risk (Youlden 2020) x 79.8% respond to induction (Pinto 2019) x 50.0% relapse (ANZCHOG 2024) x 52.0% respond post-relapse (CADTH 2021) x 30.0% enduring response (CADTH 2021 and time to treatment from Study 3b).	The studies underpinning the ANZCHOG estimate were not specific to Australia, but likely reflect reasonable estimates.
Grandfathered patients	Yr 1: █████ <sup>1</sup> (assumed)	The pre-PBAC response noted that █████ <sup>1</sup> patients were currently being treated via the EAP. .
Uptake rate	Yrs 1-6: 100% (assumed)	Reasonable
Scripts dispensed	18.78 scripts per year, 5.14 tablets per day, 1 script= 100 tablets (Study 3b Stratum 1 average for Years 1 and 2)	The same number of scripts were assumed for Stratum 1, Stratum 2 and grandfathered patients which may not be reasonable (Stratum 2 patients and grandfathered patients will likely be older and have larger BSA).
Time on treatment	2 years (Maximum time on treatment)	No discontinuation assumed, and assumed that 2 years represents time on treatment (i.e., the 2 years does not incorporate treatment breaks). Likely to overestimate time on treatment based only Study 3b, particularly for Stratum 2 patients. However, some families may want children to continue treatment beyond two years.
Eflornithine cost	DPMQ \$█████ for 1 pack of 100 tablets	Corrected DPMQs are \$█████ for 1 pack, \$█████ for 2 packs, \$█████ for 3 packs (see Requested listing).
MBS costs	7.1% patients (Study 3b Stratum 1 safety set, any hearing loss; 5.9% treatment-related used in the model) assumed to receive hearing loss diagnosis for each year of treatment at a cost of \$19.90 (\$15.92 with 80% rebate) (MBS item 82306)	MBS costs were incorrectly applied in the submission (the Stratum 1 only analysis subtracted rather than added the MBS costs, the combined Stratum 1 and 2 analysis did not include MBS costs for the Stratum 2 population) and have been corrected during the evaluation. It may also be more reasonable to assume all patients receiving eflornithine have an additional audiology appointment each year, rather than only those experiencing hearing loss. No other AEs were included, inconsistent with the economic analysis.

Source: Compiled during the evaluation from Section 4 and Excel workbook 'Eflornithine\_BIM Stratum 1 and 2 including grandfathered patients Nov\_2024.xlsx'

NBL= neuroblastoma, ABS=Australian Bureau of Statistics, ANCHOG= Australian and New Zealand Children's Haematology/Oncology Group, PSD=Public Summary Document, MSAC=Medical Services Advisory Committee, PR=partial response, CR=complete response, ORR=overall response rate, BSA=body surface area, DPMQ=dispensed price for maximum quantity, (R)PBS=(Repatriation) Pharmaceutical Benefits Scheme, MBS=Medicare Benefits Schedule

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

6.58 Table 13 summarises the estimated net financial impact to PBS and MBS of the proposed listing of eflornithine for Stratum 1 and Stratum 2 patients with HRNB who are currently in remission and who would qualify for post-maintenance therapy. The financial estimates presented below were corrected for DPMQ and MBS cost errors identified during the evaluation.

**Table 13: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimation of number of treated patients</b>						
<b>Incident NBL patients</b>	1	1	1	1	1	1
Of which, high-risk	1	1	1	1	1	1
<b>Eligible incident HRNB patients</b>						
Pts in Stratum 1	1	1	1	1	1	1
Pts in Stratum 2 refractory	1	1	1	1	1	1
Pts in Stratum 2 relapse	1	1	1	1	1	1
Pts grandfathered	1	1	1	1	1	1
<b>Total initial incident pts eflornithine</b>	1	1	1	1	1	1
<b>Estimated financial implications for the PBS/RPBS and the health budget</b>						
<b>Net change in PBS/RPBS scripts</b>						
Stratum 1 (including grandfathered)	2	2	2	2	2	2
Stratum 2 only	1	1	1	1	1	1
<b>Total</b>	2	2	2	2	2	2
<b>Net cost PBS/RPBS (less copayments)<sup>a</sup></b>						
Stratum 1 (plus grandfathered)	\$3	\$3	\$3	\$3	\$3	\$3
Stratum 2 only	\$4	\$4	\$4	\$4	\$4	\$4
<b>Total</b>	\$3	\$3	\$3	\$3	\$3	\$3
<b>Net cost to MBS</b>						
Stratum 1 (including grandfathered)	\$4	\$4	\$4	\$4	\$4	\$4
Stratum 2 only <sup>b</sup>	\$4	\$4	\$4	\$4	\$4	\$4
<b>Total<sup>b</sup></b>	\$4	\$4	\$4	\$4	\$4	\$4
<b>Net change to government budget<sup>a</sup></b>						
Stratum 1 (including grandfathered) <sup>c</sup>	\$3	\$3	\$3	\$3	\$3	\$3
Stratum 2 only <sup>b</sup>	\$4	\$4	\$4	\$4	\$4	\$4
<b>Total<sup>b</sup></b>	\$3	\$3	\$3	\$3	\$3	\$3

Source: Tables 4-5, 4-12, 4-18, 4-21 of the submission and compiled during the evaluation. Numbers rounded to nearest whole number.

inc.=including, NBL=neuroblastoma, HRNB=high-risk neuroblastoma, pt=patient, yrs=years

<sup>a</sup> DPMQ corrected to \$█ per 100 tablets (\$█ per 100 tablets in the submission)

<sup>b</sup> Corrected additional MBS costs for Stratum 2 (Stratum 2 MBS costs were not included in Table 4-22 and 4-23, pp 231-232 of the submission)

<sup>c</sup> Corrected additional MBS costs (MBS costs were deducted in Table 4-14, p224 of the submission)

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> \$0 to < \$10 million

6.59 The corrected total net cost to government over the first six years of listing was \$80 million to < 90 million for combined Stratum 1 and Stratum 2 populations and \$70 million to < \$80 million for Stratum 1 only population.

6.60 The evaluation considered that the financial estimates were uncertain due to:

- The incidence of neuroblastoma ranged from < 500 to < 500 patients per year in the submission (based on an ABS population 0-21 years (2025-2030) and

neuroblastoma incidence trend in children 0-14 years old from Youlden 2020). This exceeded previous clinical opinion and the report from the ANZCHOG (with estimates of 40-50 patients per year) and the dinutuximab beta MSAC submission which estimated 50-59 patients per year.

- Time on treatment was based on the proposed maximum time on treatment of 2 years. The time on treatment for Stratum 2 and grandfathered patients may be overestimated, given the lower EFS rate and lower remaining treatment time for Stratum 2 and grandfathered patients, respectively, compared to Stratum 1 patients. Mean time on treatment in the economic analysis was 627.1 days compared to 730.5 days in the financial estimates. The PBAC noted reducing the time on treatment to 627.1 days, consistent with the economic model, decreased the cost to the government budget by 13%.
- The rate of responding to consolidation therapy did not include the probability of completing consolidation therapy, likely overestimating the number of patients in Stratum 1. However, the sources for Stratum 1 eligibility are generally uncertain; the proposed sources and Study 3b reported different response rates for all stages of treatment (induction, consolidation, maintenance). Therefore, it is unclear whether the combined proportion of eligible patients was likely over or underestimated.
- The proportion of HRNB patients expected to ever experience relapse was 50% in the financial estimates from the ANZCHOG, compared to 30.8% in the SOC arm of the Stratum 1 economic analysis. This may reflect a fitter population in the PSM adjusted Study ANBL0032 population compared to all HRNB patients, however it demonstrates there is uncertainty in the estimate of relapsed patients.
- The proportion of relapsed patients responding to initial relapse therapy was based on response to dinutuximab beta in combination with irinotecan plus temozolomide (CADTH 2021). Currently this is not funded in Australia, although is being considered by MSAC (<https://www.msac.gov.au/applications/1791>).
- The proportion of relapsed patients who were eligible to receive eflornithine after responding to initial relapse therapy was 30%, based on time between completing treatment and starting eflornithine in Study 3b (i.e., the probability of an enduring response). In practice, with eflornithine available on the PBS, this time may reduce, and more patients post relapse may have access to eflornithine upon completion of their therapy.
- The dose was based on the weighted number of tablets per person from Study 3b Stratum 1, and it appeared to be estimated according to expected BSA for patients (as per the economic analysis), and not on reported numbers of tablets taken. As such there may be uncertainty in the dose if treatment breaks occurred.

6.61 The DUSC considered the estimates presented in the submission to be overestimated. The main issues were:

- The proportion of incident neuroblastoma patients was overestimated and DUSC agreed with the commentary that it is not appropriate to apply the same incidence rate to 15-21 year olds who have a much lower incidence than ages 0-14 years. The DUSC considered a more reasonable estimate would be in the range of < 500 to < 500 incident patients and noted the PSCR agreed with this revision. The PBAC noted this resulted in a reduction in net cost of 47% over 6 years.
- The DUSC agreed with the commentary and considered the incidence rate of 10.6 patients per million children to be high and unverified. DUSC considered 9.5 patients per million children (as reported in Youlden 2020) was a more reasonable estimate.
- The DUSC considered that response rates for induction and consolidation were potentially overestimated.
- The DUSC considered that time on treatment (2 years) was likely overestimated due to potential for relapse and adverse events, and that children grandfathered from the Federally funded and EAP programs may not require the full two-year duration of treatment. However, DUSC considered this overestimate may be balanced by use in patients/families wishing to continue treatment beyond 2 years. The PBAC noted that the restriction for eflornithine should specify treatment for no longer than 27 cycles [equivalent to 2 years] from the first dose (excluding treatment breaks); therefore, treatment beyond the intended duration would be unlikely.

6.62 Quality Use of Medicines information:

- The DUSC noted the submission did not present any factors for quality use of medicines though advised that the requirement for 3-monthly reassessments of BSA should be reinforced. The Secretariat commented that at the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' BSA and only 3 months of therapy will be provided with each script. The written authority must include the patient's BSA measurement.
- The DUSC advised that safety and monitoring of adverse effects such as audiology tests will be required.
- The DUSC considered that eflornithine will be used mainly in highly specialised settings, but there may be some instances where less specialised practitioners may use this medicine in regional or rural areas. The Secretariat commented that patients must be initially treated in a hospital/cancer centre by either a paediatric oncologist or haematologist, and continuing treatment must occur at least under direct supervision of a paediatric oncologist or haematologist.

- The DUSC advised that specific advice around administering crushed tablets to children will be required.

### **Financial Management – Risk Sharing Arrangements**

6.63 No risk sharing arrangement (RSA) was presented in the submission. However, the PSCR stated that the Sponsor is open to a RSA to ensure access to therapy.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of eflornithine for post-maintenance treatment to prevent relapse in patients with high-risk neuroblastoma (HRNB) who are in remission after receiving multiagent, multimodality therapy. The PBAC acknowledged the high clinical need for a post-maintenance treatment to prevent relapse of this condition. The PBAC considered that eflornithine provides a clinical benefit for patients compared to standard of care (SOC), and while the magnitude of benefit was uncertain, the PBAC acknowledged the difficulty of obtaining high quality clinical evidence in this patient group. The PBAC considered that the ICER was high and uncertain, partly because the submission's assumptions about the duration of benefit (extrapolation and time horizon) were optimistic. The PBAC considered that a more conservative time horizon would be required along with a price reduction to achieve an acceptable ICER. The PBAC considered the estimated number of incident neuroblastoma patients was overestimated and should be reduced to < 500 to < 500 patients year.
- 7.2 The PBAC is satisfied that eflornithine provides, for some patients, a significant improvement in efficacy over the main comparator, SOC, in the post-maintenance treatment of HRNB, albeit with inferior safety.
- 7.3 The PBAC noted the high clinical need for a post-maintenance treatment in HRNB, commenting that there is a high rate of relapse following upfront therapy and that current salvage treatments are toxic with low efficacy. The PBAC noted the high number of consumer comments detailing the high burden of disease and suffering associated with HRNB, as well as the prohibitive cost of eflornithine.
- 7.4 The PBAC noted the proposed listing was for patients with HRNB who are in remission (i) at the end of upfront therapy; or (ii) after any previous treatment for relapsed or refractory disease. The PBAC considered it would be appropriate to not differentiate the populations in the listing and make eflornithine available for patients in remission after receiving multiagent, multimodality therapy, consistent with the proposed TGA indication. The PBAC noted this use of eflornithine (i.e., following multiagent, multimodality therapy) is referred to as post-maintenance treatment.
- 7.5 The PBAC noted the following points regarding the restriction for eflornithine. The reasoning behind each point is discussed in paragraphs 3.2 to 3.12.

- That patients in remission at the end of multiagent, multimodality therapy should have access to eflornithine via the PBS;
  - That patients cannot be re-treated with eflornithine.
  - That eflornithine should be listed on the Highly Specialised Drugs Section 100 schedule;
  - That it is unnecessary to specify the minimum age of patients;
  - That initial and continuing restrictions would be required, with approximately < 500 grandfathered patients from the Sponsor’s EAP able to enter PBS-treatment via a grandfather restriction;
  - The clinical criterion “Patient must not have developed disease progression while receiving treatment with this drug for this condition” is amended to “Patient must not have developed disease recurrence while receiving treatment with this drug for this condition”;
  - That treatment interruptions should not be counted towards the maximum 2-year (27 cycles) treatment timeframe;
  - That treatment must be initiated by a paediatric oncologist or haematologist and can be continued under direct supervision of a paediatric oncologist or haematologist;
  - That there should not be a requirement to initiate eflornithine therapy within 120 days after completing previous therapy for HRNB; and
    - That the date of commencement and duration of prior multiagent, multimodality therapy is described in the initial application; and
    - That particular risk classification system/s for neuroblastoma should not be specified.
- 7.6 The PBAC accepted the proposed clinical place for eflornithine as post-maintenance therapy in HRNB and noted that there are no approved therapies designated for post-maintenance treatment. The PBAC accepted the nominated comparator of SOC, which is follow up and monitoring. The PBAC noted that eflornithine would not replace any medicine but be used in addition to current SOC.
- 7.7 The PBAC noted that the pivotal trial evidence presented in the submission (Study 3b), was based on a single-arm trial of eflornithine in post-maintenance treatment of HRNB patients in remission at the end of upfront therapy (Stratum 1) or after therapy for refractory/relapsed disease (Stratum 2). The single-arm eflornithine data were compared to historical controls from the ANBL0032 study (for Stratum 1) and Santana 2008 (for Stratum 2). A propensity score matched (PSM) study involved Stratum 1 patients from Study 3b, which compared eflornithine to historical controls from Study ANBL0032 while controlling for baseline covariates.

- 7.8 Results for Stratum 1 patients were informed by Study 3b and the PSM study. The PBAC noted that patients treated with eflornithine had numerically improved EFS and OS event rates compared to unadjusted historical control data from Study ANBL0032, however considered that the comparison was not informative. The PBAC considered there was a high risk of bias, given that the historical controls included patients not in remission and who were treated up to two decades prior to the patients in Study 3b. The PBAC noted that the PSM study found a significant treatment effect at a median follow-up of over 5 years for EFS (EFS at 48 months of 84% vs 72%, HR 0.49; 95%CI 0.28, 0.86) and OS (OS at 48 months of 96% vs 85%, HR 0.33; 95%CI 0.16, 0.70), albeit with a moderate degree of potential bias due to residual confounding from unmeasured covariates, and with wide confidence intervals and sensitivity to study assumptions. However, on balance, the PBAC was satisfied that the claim of superiority compared to SOC with respect to efficacy was reasonable for Stratum 1 patients.
- 7.9 Results for Stratum 2 patients were informed by Study 3b; no PSM analysis was available for this group. While the PBAC noted that patients treated with eflornithine had numerically improved EFS event rates compared to unadjusted historical control data from Santana 2008, it considered the results to be associated with a high risk of bias and the claim of superiority over SOC to be uncertain.
- 7.10 Overall, the PBAC considered eflornithine offered moderate clinical benefit for HRNB, with moderate certainty for Stratum 1 patients but low certainty for Stratum 2 patients. The PBAC acknowledged the difficulty of obtaining high quality clinical evidence in HRNB and the lack of treatment options available, particularly for the relapsed/refractory Stratum 2 patients.
- 7.11 The PBAC agreed with the submission that eflornithine has an inferior safety profile compared to SOC, given the warnings for hepatotoxicity, myelosuppression, and hearing loss, and noting the registration requirements with respect to safety set out in the TGA Delegate's Overview.
- 7.12 The PBAC noted the corrected base case ICER for Stratum 1 patients in the submission was \$155,000 to < \$255,000 per QALY gained. While the PBAC considered that the economic model for Stratum 1 was generally reliable for decision-making, the PBAC noted that the ICER was sensitive to inputs that affected EFS and OS benefit and considered it to be uncertain. The PBAC agreed with the ESC that the uncertainty was largely driven by the quality of the available eflornithine clinical data, with the reliance on the PSM analysis with small patient numbers, and relatively short follow-up. The PBAC considered that the submission's time horizon of 100 years was unrealistic compared to the length of the study data (7.21 years in Study 3b Stratum 1 and 5.85 years in Study ANBL0032); the PBAC considered that a time horizon of 50 years would be appropriate. The PBAC advised that an ICER of \$95,000 to < \$115,000 per QALY gained would be reasonable considering the uncertainty associated with the issues described above.

- 7.13 The PBAC considered the economic model to be unreliable for the small number of relapsed/refractory patients who achieved remission prior to post-maintenance therapy (Stratum 2). In the absence of any likely forthcoming clinical evidence for this small patient group with a high clinical need, the PBAC accepted that the cost-effectiveness of eflornithine in Stratum 2 was likely to be comparable to patients in Stratum 1 given that patients in both strata were in remission when eflornithine was commenced.
- 7.14 The PBAC noted the submission used an epidemiological approach to estimate the financial impact of listing eflornithine. The PBAC noted the approach likely overestimated the incidence of neuroblastoma (see paragraph 6.62) and therefore the incidence of HRNB. The PBAC advised the incidence of neuroblastoma should be < 500 to < 500 patients per year and this would result in approximately < 500 to < 500 HRNB patients initiating treatment with eflornithine per year. The PBAC advised the average treatment duration should be reduced from 2 years to 1.72 years for consistency with the economic model (see paragraph 6.61). The PBAC advised the treatment duration for the < 500 patients expected to transition to PBS subsidised treatment should be assumed to be less than 1.72 years to account for treatment already received.
- 7.15 The PBAC considered that, with the amendments to the restriction criteria outlined in paragraph 7.5, there was minimal risk of use outside the proposed patient population and a risk sharing arrangement was not required.
- 7.16 The PBAC recommended that eflornithine should not be treated as interchangeable with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.
- 7.17 The PBAC advised that eflornithine is not suitable for prescribing by nurse practitioners. The PBAC advised that eflornithine is suitable for prescribing by medical practitioners only.
- 7.18 The proposed dosing schedule is based on BSA, which is likely to change particularly in young children. Based on this, the PBAC advised the Early Supply Rule should not apply.
- 7.19 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for eflornithine:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies on the basis of superior comparative effectiveness over SOC;
  - b) The treatment is expected to address a high and urgent unmet clinical need due to the lack of any treatment options for relapse prevention of HRNB;
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

Add new item:

### Initial Restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EFLORNITHINE					
Eflornithine, 250 mg tablet, 100	NEW	3	300	2	Ifinwil
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (FULL assessment - written)					
<b>Authority type:</b> <input checked="" type="checkbox"/> Complex Authority Required (CAR)					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply					
<b>Episodicity:</b> n/a					
<b>Severity:</b> High-risk					
<b>Condition:</b> Neuroblastoma					
<b>Indication:</b> High-risk neuroblastoma					
<b>Treatment Phase:</b> Initial Treatment					
<b>Clinical criteria:</b>					
Patient must have high risk neuroblastoma according to a validated risk classification system					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must be in remission, with at least a partial response, at the end of multiagent, multimodality therapy for high-risk neuroblastoma					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must be initiated after completing previous therapy					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
<b>Treatment Criteria:</b>					
Must be treated in a hospital/cancer centre by either a: (i) paediatric oncologist (ii) haematologist;					
<b>Prescribing Instructions:</b> Prior to initiating treatment with this drug, a complete blood count, liver function tests and baseline hearing assessments should be performed and documented in the patients' medical records.					

**Prescribing Instructions:**

At the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' Body Surface Area (BSA), according to the dosing schedule in the TGA approved Product Information.

The following number of packs and repeats may be authorised under this restriction (providing 3 months of therapy for each prescription).

Up to a maximum quantity of 100 units and 1 repeat for a BSA 0.25 to <0.5 m<sup>2</sup>

Up to a maximum quantity of 200 units and 1 repeat for a BSA 0.5 to <0.75 m<sup>2</sup>

Up to a maximum quantity of 200 units and 2 repeats for a BSA 0.75 to 1.5 m<sup>2</sup>

Up to a maximum quantity of 300 units and 2 repeats for a BSA >1.5 m<sup>2</sup>

**Prescribing Instructions:**

Authority applications for initial treatment must be made in writing and must include:

(a) details of the proposed prescription; and

(b) a completed PBS authority application form, relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following:

(i) details of prior multiagent, multimodality therapy for high-risk neuroblastoma [date of commencement and duration of therapy]; and

(iii) the patients' BSA measurement

**Administrative Advice:**

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](http://www.servicesaustralia.gov.au)

Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos)

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EFLORNITHINE					
Eflornithine, 250 mg tablet, 100	NEW	3	300	2	Ifinwil
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Immediate assessment (Telephone/Online)					
<b>Authority type:</b> <input checked="" type="checkbox"/> Complex Authority Required (CAR)					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
<b>Indication:</b> High-risk neuroblastoma					
<b>Treatment Phase:</b> Continuing Treatment					
<b>Clinical criteria:</b>					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					

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<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have developed disease recurrence while receiving treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed a total of 27 cycles (based on 4 weeks per cycle) from the first dose of this drug, regardless of whether it was PBS/non-PBS subsidised
<b>Treatment Criteria:</b>
Must be treated in a hospital/cancer centre by either a: (i) paediatric oncologist (ii) haematologist; or
Must be treated by a medical practitioner under the direct supervision of either a: (i) paediatric oncologist (ii) haematologist
<b>Prescribing Instructions:</b>
At the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' Body Surface Area (BSA), according to the dosing schedule in the TGA approved Product Information.
The following number of packs and repeats may be authorised under this restriction (providing 3 months of therapy for each prescription).
Up to a maximum quantity of 100 units and 1 repeat for a BSA 0.25 to <0.5 m <sup>2</sup>
Up to a maximum quantity of 200 units and 1 repeat for a BSA 0.5 to <0.75 m <sup>2</sup>
Up to a maximum quantity of 200 units and 2 repeats for a BSA 0.75 to 1.5 m <sup>2</sup>
Up to a maximum quantity of 300 units and 2 repeats for a BSA >1.5 m <sup>2</sup>
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>
<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Immediate assessment (Telephone/Online)
<b>Authority type:</b> <input checked="" type="checkbox"/> Complex Authority Required (CAR)
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply
<b>Indication:</b> High-risk neuroblastoma
<b>Treatment Phase:</b> Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment
<b>Clinical criteria:</b>
<b>Clinical criteria:</b> Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing]
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have developed disease recurrence while receiving treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed a total of 27 cycles (based on 4 weeks per cycle) from the first dose of this drug, regardless of whether it was PBS/non-PBS subsidised
<b>Treatment Criteria:</b>
Must be treated in a hospital/cancer centre by either a: (i) paediatric oncologist (ii) haematologist; or
Must be treated by a medical practitioner under the direct supervision of either a: (i) paediatric oncologist (ii) haematologist

**Prescribing Instructions:**

At the time of the authority application, the prescriber should request an appropriate number of packs and repeats based on the patients' Body Surface Area (BSA), according to the dosing schedule in the TGA approved Product Information.

The following number of packs and repeats may be authorised under this restriction (providing 3 months of therapy for each prescription).

Up to a maximum quantity of 100 units and 1 repeat for a BSA 0.25 to <0.5 m<sup>2</sup>

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Up to a maximum quantity of 200 units and 2 repeats for a BSA 0.75 to 1.5 m<sup>2</sup>

Up to a maximum quantity of 300 units and 2 repeats for a BSA >1.5 m<sup>2</sup>

**Administrative Advice:** A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.

**Administrative Advice:** This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The Sponsor welcomes the PBAC recommendation, which facilitates access to a post-maintenance treatment option for HRNB on the PBS.