Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Nelarabine-Reach

Active ingredient: Nelarabine

Sponsor: Reach Pharmaceuticals Pty Ltd

August 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse events
ALL	Acute lymphoblastic leukemia
alloSCT	allogeneic stem cell transplantation
Ara-G	9-b-D-arabinofuranosylguanine, Nelarabine
Ara-GTP	ara-G triphosphate
ARTG	Australian Register of Therapeutic Goods
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero to time t
BM	Bone marrow
CI	confidence interval
CL	clearance
CL/F	apparent clearance (L/day)
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete remission
CRe	Complete response
CRi	incomplete remission
CR+CRi	Complete remission with or without hematologic recovery
CSF	cerebrospinal fluid
CV	co-efficient of variation
DLP	Data lock point
LBL	Lymphoblastic lymphoma
MRD	Minimal Residual Disease
MTD	Maximal tolerated dose
ORR	Overall response rate
OS	Overall survival
PD	pharmacodynamics
PI	Product information
PK	pharmacokinetic

Abbreviation	Meaning
PR	Partial response
PSUR	Periodic safety update report
R/R	Relapsed or refractory
RMP	Risk management plan
T-ALL	T-cell acute lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
TGA	Therapeutic Goods Administration
V_{SS}	Volume of distribution at steady state

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Nelarabine-Reach
Active ingredient:	Nelarabine
Decision:	Approved
Date of decision:	25 March 2024
Date of entry onto ARTG:	3 April 2024
ARTG number:	405072
, *Black Triangle Scheme*	Yes
sponsor's name and address:	Reach Pharmaceuticals Pty Ltd, Corporate One, 84 Hotham Rd, Preston VIC 3072
Dose form:	clear colourless solution
Strength:	Each vial contains 250 mg of nelarabine in 50 mL of solution. Each mL of solution contains 5 mg of nelarabine.
Container:	Glass vial
Pack size:	Each vial contains 50 ml of solution. NELARABINE-REACH is supplied in packs of 1 vial or 6 vials.
Approved therapeutic use for the current submission:	Nelarabine is indicated for the treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.
Route of administration:	Intravenous
Dosage:	**Adults and adolescents (aged 16 years and older)** The recommended dose of nelarabine for adults and adolescents aged 16 years and older is 1,500 mg/m^2 administered intravenously over two hours on days 1, 3 and 5 and repeated every 21 days. **Children and adolescents (aged 21 years and younger)** The recommended dose of nelarabine for children and adolescents (aged 21 years and younger) is 650 mg/m^2 administered intravenously over one hour daily for 5 consecutive days, repeated every 21 days.

	For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	Category D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects There are no or limited amount of data from the use of nelarabine in pregnant women. Animal data indicate that exposure during pregnancy will likely lead to malformations of the fetus. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Nelarabine-Reach

This AusPAR describes the submission by Reach Pharmaceuticals Pty Ltd (the sponsor) to register Nelarabine-Reach for the following proposed indication:[1]

> *Nelarabine-Reach is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma.*

T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL).

Acute lymphoblastic leukemia (ALL) is a type of B or T lymphoblastic malignancy defined by the rapid proliferation of abnormal, immature lymphocytes, and their precursors which eventually leads to the replacement of bone marrow and other lymphoid organs. Acute lymphoblastic lymphoma (LBL) is commonly considered the lymphomatous variant of ALL in which extramedullary disease predominates in the presence of lesser involvement (< 25% marrow blasts) of the bone marrow compared with ALL. ALL and LBL are aggressive diseases that progress rapidly to a fatal outcome in the absence of effective therapy.

An important subset of ALL and LBL is the T-cell lineage form of the disease which is less frequent than B-cell lineage disease. T-cell lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) are characterised by massive infiltration of immature T cells mainly in the mediastinum and other lymphoid organs with or without involvement of

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

peripheral blood, bone marrow (BM) and cerebral spinal fluid (CSF) compartments. T-ALL accounts for 15% of the ALL cases, whereas T-LBL represents approximately 25-30% of the non-Hodgkin lymphomas in children and adolescents[2]. T-ALL and T-LBL are considered the same disease differentiated only by the extent of bone marrow infiltration[3].

Globally, ALL represents 12% of all leukaemia cases with global incidence ranging from 1 to 4.75 per 100,000 people. T-ALL accounts for 12-15% of child cases of ALL and up to 25% of adult cases of ALL. Amongst the paediatric population, the median age of onset is 9 years and adolescents are most commonly affected. Furthermore, males have 3-fold increased risk of developing T-ALL compared to females. The incidence of ALL in Australia is 1.5 per 100,000 population with prevalence of around 375 people.

It has been reported that approximately 40% of relapsed T-LBL patients had evidence of BM involvement, whereas less than 20% of the T-LBL patients presented with BM involvement at diagnosis[4]. Relapses in T-ALL patients present differently with 15% to 20% of the relapses occurring in apparent isolated extramedullary compartments, mostly in the central nervous system (CNS) or the testis with no or low blast counts (<5%) in BM biopsies[5]. Prognosis in T-ALL is impacted by several factors, including age, CNS involvement, certain chromosomal/genetic abnormalities and minimal residual disease (MRD) status[6]. The main clinical prognostic factor for T-LBL appears to be localised vs advanced disease[7]. Historically, older adolescents and young adults have a poorer prognosis than young children. However, recent advances and collaborative group studies have substantially improved strategies for personalised treatment by identifying new targets for therapeutic intervention[8].

Current treatment options for T-ALL and T-LBL

The T-cell lineage forms of ALL (T-ALL and T-LBL) are considered high risk diseases requiring more aggressive therapy. For T-ALL patients, the major treatment options are chemotherapy regimens like Children's Oncology Group protocol and/or stem cell transplantation (SCT). Similar treatment strategies are followed for patients with T-LBL. Newly diagnosed T-ALL and T-LBL patients are typically treated with induction therapy consisting minimally of vincristine, prednisone, and anthracycline with or without asparaginase. Utilizing modern risk adapted treatment plans in these patients; the complete response (CR) rate is > 95% in children and 60-80% in adults. Induction therapy is followed by additional cycles of multi-agent chemotherapy incorporating substances of different drug classes with the aim of long-term disease control. Despite high rates of complete remission (CRe) with modern chemotherapy regimens, the prognosis of ALL has not altered in the last two to three decades[9].

[2] Kroeze, E., Loeffen, J. L., Poort, V. M., & Meijerink, J. P. (2020). T-cell lymphoblastic lymphoma and leukaemia: different diseases from a common premalignant progenitor?. Blood Advances, 4(14), 3466-3473.

[3] Hoelzer, D., Thiel, E., Arnold, R., Beck, J., Beelen, D. W., Bornhäuser, M., ... & Gökbuget, N. (2009). Successful subtype oriented treatment strategies in adult T-All; results of 744 patients treated in three consecutive GMALL studies. Blood, 114(22), 324.

[4] Burkhardt, B., & Hermiston, M. L. (2019). Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. British Journal of Haematology, 185(6), 1158-1170.

[5] Kroeze et al, 2020

[6] National Cancer Institute (2017) Adult acute lymphoblastic leukemia treatment (PDQ_)–health professional version. Available at: https://www.cancer.gov/types/leukemia/hp/adult-all-treatmentpdq (Accessed 7 March 2017).

[7] National Cancer Institute (2016) Childhood non- Hodgkin lymphoma treatment (PDQ_)–health professional version. Available at: https://www.cancer.gov/types/lymphoma/hp/child-nhl-treatmentpdq .

[8] Pui, C.H., Yang, J.J., Hunger, S.P., Pieters, R., et al. (2015) Childhood acute lymphoblastic leukemia: progress through collaboration. Journal of Clinical Oncology, 33, 2938–2948.

[9] Kathpalia M, Mishra P, Bajpai R, Bhurani D, Agarwal N. Efficacy and safety of nelarabine in patients with relapsed or refractory T-cell acute lymphoblastic leukemia: a systematic review and meta-analysis. Ann Hematol. 2022 Aug;101(8):1655-1666. doi: 10.1007/s00277-022-04880-1. Epub 2022 Jun 21. PMID: 35727338.

25-30% of children experience relapse or are refractory to initial induction therapy with a resultant poor prognosis. Children who relapse within 6 months of completion of initial therapy show a 10% to 20% likelihood of long-term survival when treated with chemotherapy alone while those who relapse ≥ 1year from completion of therapy have a 30% to 40% probability of long-term survival. The cure rate of T-ALL and T-LBL in adults is lower than in children and majority of adult patients will eventually experience relapse after first CR.

There is lack of consensus for therapy of patients with relapsed or refractory (R/R) disease and it is individualised based on the nature of response to prior therapy (e.g., achieve CR or not, timing of relapse following CR, total anthracycline dose received, any agent specific toxicity). Clofarabine is the only currently approved agent in Europe for single-agent therapy in R/R paediatric ALL. However, most patients with first relapse will receive multi-agent combination re-induction therapy, which has demonstrated CR rates above 80% in children and ranging from 30-76% in adults.

Patients when treated with haemotherapy alone even if achieving a second remission have a poor prognosis and these patients are recommended for re-induction chemotherapy followed by allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT) for those who have an HLA-matched donor or autologous transplantation for those who do not. Patients in second relapse would normally have received at least two multi agent chemotherapy regimens without having reached a sufficiently stable remission of their disease. Furthermore, use of intensive chemotherapy in R/R ALL is associated with increased risk of infections and a higher mortality rate resulting in lack of long-term remission and limiting a transition to SCT. Long-term event free survival rates as high as 70% have been reported in children after BMT, while the probability for long-term survival in adult patients with relapsed ALL is lower, even with BMT. The benefit of any new antileukaemic agent must be assessed in the context that only CR or at least a very substantial reduction in leukaemic blasts would be of therapeutic interest and that achievement of CR should be followed by additional chemotherapy and/or BMT when feasible[10].

Clinical rationale for nelarabine therapy of T-ALL and T-LBL

Nelarabine is an antineoplastic agent that acts as DNA synthesis inhibitor. The development of nelarabine began with the observation that intracellular deoxyguanosine (dGuo) triphosphate (dGTP) accumulation was specifically toxic to T-cells in patients with the inherited immunodeficiency syndrome purine nucleoside phosphorylase (PNP) deficiency. Although there was evidence that the deoxyguanosine analogue arabinofuranosylguanine (ara-G) was toxic to T-cells and might be beneficial in the treatment of T-cell malignancies, its clinical evaluation was limited due to its low water solubility. Nelarabine is the water-soluble prodrug of the deoxyguanosine analogue ara-G. Following intravenous administration, it is rapidly demethylated to 9-b-D-arabinofuranosylguanine (ara-G) by adenosine deaminase. The monophosphate metabolite is subsequently converted to the active 5'-triphosphate from, ara-GTP. Ara-GTP preferentially accumulates in cancerous T-cells, is incorporated into DNA causing inhibition of DNA synthesis and cell death.

Nelarabine was first synthesised in the late 1970s and received FDA approval in 2005 (EU approval in 2007) for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) that has not responded to or has relapsed after treatment with at least two chemotherapy regimens. Dose-dependent toxicities, including neurotoxicity

[10] Kathpalia *et. al.*, 2022

and myelosuppression associated with nelarabine treatment are potential barriers to its use for treatment of T-ALL/T-LBL[11]. Since its initial approval in 2005, numerous studies have been reported to elucidate the appropriate use of nelarabine for refractory haematologic malignancies.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

An application for Nelarabine was made to the FDA

ARRANON (nelarabine 5mg/ml solution for infusion; Novartis) and ATRIANCE (nelarabine 5mg/ml solution for infusion; Sandoz Pharmaceuticals) have been approved in the US and EU.

US

ARRANON (nelarabine 5mg/ml solution for infusion) received FDA approval in 2005 for following indication: *"ARRANON is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomised trials demonstrating increased survival or other clinical benefit have not been conducted."*

The current FDA approved indication (revised 7/2019) is as follows: *"ARRANON is a nucleoside metabolic inhibitor indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in adult and paediatric patients aged 1 year and older whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens".*

It is noted that post-marketing requirement PMR 1284-1 ("Submit the results of the proposed Phase 3 trial (AALL0434) to be conducted by the Children's Oncology Group to demonstrate nelarabine's clinical benefit") was reviewed and concluded to be fulfilled on 31 July 2019. see NDA 021877/S-010 Supplement Approval.

EU

Atriance (nelarabine 5mg/ml solution for infusion) was approved in EU in 2007 for the following indication: *"Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data."*

[11] Candoni, A., Lazzarotto, D., Ferrara, F., Curti, A., Lussana, F., Papayannidis, C., & Foà, R. (2020). Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukaemia/lymphoma. A CAMPUS ALL study. American journal of hematology, 95(12), 1466-1472

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for Nelarabine Reach submission PM-2023-00623-1-6

Description	Date
Designation (Orphan)	6 December 2022
Submission dossier accepted and first round evaluation commenced	31 March 2023
Evaluation completed	28 November 2023
delegate's[12] Overall benefit-risk assessment and request for Advisory Committee advice.	20 December 2023
Advisory Committee meeting	16 February 2024
Registration decision (Outcome)	25 March 2024
Registration in the ARTG	3 April 2024
Number of working days from submission dossier acceptance to registration decision*	355

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Quality

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

A number of deficiencies in the application data were identified relating to the PI, labelling, and impurities in the drug substance which were all satisfactorily resolved prior to approval.

The stability data provided is sufficient to support the proposed shelf life of 18 months when stored below 25 °C in the commercial packaging.

The evaluator was satisfied that the sponsor had satisfied all requirements with respect to:

- stability and release specifications (which dictate the medicine's physicochemical properties, biological activity/potency, immunochemical properties and purity)
- appropriately conducted stability studies that support the proposed shelf life/storage conditions.

[12] The 'delegate' is the delegate of the Secretary of the Department of Health and Aged Care who made the final decision to either include the new medicine/indication on the ARTG or reject the submission, under section 25 of the Therapeutic Goods Act

- validation of analytical procedures utilised to assess drug specifications.
- appropriate choice/synthesis and validation of reference standards and reference materials
- appropriate in-process controls within the manufacturing process and identification of critical manufacturing steps
- consistency of medicine manufacture verified by process validation and demonstrated through batch analysis
- satisfactory control of impurities.
- adequate characterisation and justification of excipients
- medicine sterility/appropriate control of infectious disease & adventitious agents.
- appropriate/compatible container closure systems
- labelling that conformed to Therapeutic Goods Order 91.

Nonclinical

The nonclinical submission was entirely literature-based, and adequate in scope. All pivotal safety-related studies were GLP-compliant.

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G). Nelarabine is demethylated by adenosine deaminase to form ara-G, which is then mono- phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase; the monophosphate metabolite is subsequently converted to the active 5′-triphosphate form, ara-GTP. Accumulation of ara-GTP in malignant cells results in preferential incorporation into DNA where it acts as a chain terminator, inhibiting DNA synthesis, which results in cell death. Ara-G is also able to induce apoptosis in T cells by involvement of Fas/FasL system, resulting in release of soluble FasL and triggering death receptor-mediated cell death in the bystander cells.

Cytotoxicity to various malignant human T-cell lines was demonstrated for nelarabine (and ara-G) *in vitro*, and anti-tumour activity was demonstrated for the drug *in vivo* in T-ALL tumour-bearing mice. These primary pharmacology studies offer support for the utility of nelarabine for the proposed indication.

ECG was shown to be unaffected in nelarabine-treated monkeys.

Nelarabine is rapidly converted to ara-G in laboratory animal species and humans. The plasma half-life of ara-G is also short. Plasma protein binding by nelarabine and ara-G is low. Rapid and wide tissue distribution of ^{14}C-nelarabine-derived radioactivity was demonstrated in mice. Limited penetration of the blood-brain barrier was evident; binding to melanin was not apparent. Metabolism of nelarabine involves O-demethylation by adenosine deaminase to form ara-G. Other metabolites — formed from hydrolysis, demethylation, de-amination and further oxidation — include methylguanine, guanine, xanthine, uric acid and allantoin. Excretion was shown to be predominantly via the urine in mice and monkeys.

In vitro experiments revealed no CYP inhibition or induction, and no transport by or inhibition of P-glycoprotein, for either nelarabine or ara-G.

Maximum observed non-lethal doses by the IV route in single-dose toxicity studies in mice, dogs and monkeys were the highest doses tested, representing 1.2-, 4.8- and 4-fold the maximum recommended human dose on a body surface area-adjusted basis.

Pivotal repeat-dose toxicity studies involved daily IV administration in mice (5 days) and monkeys (up to 30 days). Key findings comprised neurotoxicity, and effects on gastrointestinal and lymphoid tissues and on bone marrow.

There were two distinct types of neurotoxicity observed in the repeat-dose toxicity program: rapidly developing and likely related to some action of nelarabine at a secondary pharmacological target (observed in mice and in ketamine-anaesthetised monkeys), and slower developing and seen to relate to accumulation of intracellular ara-GTP in neurons (monkeys). Findings comprised seizures, convulsions, muscle tremor and weakness, in-coordination, ataxia, depth perception deficits and unresponsiveness. Neurotoxicity so severe as to be fatal or to prompt euthanasia was associated with histopathological lesions in the CNS (white matter degeneration and vacuolation in cerebrum, cerebellum and spinal cord) in monkeys. Neurotoxicity was at least partially reversible in survivors. The slower developing neurotoxicity in monkeys is seen to resemble the Guillain-Barré-like syndrome seen in patients.

Targeting of mitotically active cells in the gastrointestinal tract, lymphoid organs and bone marrow was evident for nelarabine, and is recognised as a class effect.

Nelarabine was demonstrated to be genotoxic, with positive results returned in assays using L5178Y/TK mouse lymphoma cells in both the absence and presence of metabolic activation.

Carcinogenicity studies were not performed and are not required for a medicine indicated for the treatment of advanced cancer.

Teratogenicity was demonstrated with nelarabine in rabbits, with this encountered in the absence of maternotoxicity and at exposure levels well below that of patients. Assignment to Pregnancy Category D, as proposed by the sponsor, is supported.

The toxicological profile of nelarabine has been adequately characterised to aid the safe use of nelarabine in patients. Neurotoxicity is identified as the key relevant concern.

There are no objections on nonclinical grounds to the proposed registration of Nelarabine-Reach for the proposed indication.

Clinical

This was a literature-based submission.

Pharmacology

The main PK findings from the clinical evaluator were from review of the literature reports provided. None of the PK or pharmacodynamic studies were conducted by the sponsor.

Summary of key findings from clinical pharmacology assessment:

Pharmacokinetics summary:

- After intravenous (IV) administration of nelarabine, all the dose is rapidly converted to ara-G; approximately 94% of an administered dose being converted to ara-G by the end of a 1-hour infusion.
- After infusion of 1,500 mg/m^2 nelarabine over two hours in adult patients, mean (%CV) plasma nelarabine Cmax and AUCinf values were 13.9 µM (81%) and 13.5 µM.h (56%) respectively. Mean plasma ara-G Cmax and AUCinf values were 115 µM (16%) and 571 µM.h (30%), respectively.

- After infusion of 400 or 650 mg/m^2 nelarabine over one hour in 6 paediatric patients, mean (%CV) plasma nelarabine Cmax and AUCinf values, adjusted to a 650 mg/m^2 dose, were 45.0 µM (40%) and 38.0 µM.h (39%), respectively. Mean plasma ara-G Cmax and AUCinf values were 60.1 µM (17%) and 212 µM.h (18%), respectively.
- Nelarabine and ara-G are not bound to human plasma proteins (less than 25 %) *in vitro*, and binding is independent of nelarabine or ara-G concentrations up to 600 µM.
- The pharmacokinetics (PK) of ara-G were similar on days 2 and 5 of a 5-day course, indicating that ara-G did not accumulate during the treatment regimen, which is not unexpected, as the $t_{1/2}$ of ara-G is sufficiently short to allow for its elimination prior to a subsequent dose.
- In special patient populations:
  - The CL of ara-G is higher in pediatric patients as compared with adult patients and may to be related to renal function
  - The PKs of nelarabine and ara-G were similar in male and female adult patients
  - PKs of nelarabine or ara-G were similar in patients with different haematologic diagnoses although interpretation was limited by small number of patients with each diagnosis
  - Limited PK data is available in children aged < 4 years and adults aged >65 years
  - There is lack of data in patients with moderate/severe renal impairment
  - PKs of nelarabine/ara-G were not evaluated in patients with hepatic impairment
- Drug-drug interactions:
  - Nelarabine and ara-G did not significantly inhibit the activities of the major hepatic cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*
  - Concomitant administration of nelarabine in combination with adenosine deaminase inhibitors such as pentostatin is not recommended as it may reduce the efficacy or change safety profile of nelarabine
  - Administration of fludarabine 30 mg/m^2 given as a 30-minute infusion, 4 hours prior to nelarabine (1200mg/m^2) did not affect the PKs of nelarabine, ara-GTP in 12 patients with refractory leukaemia

Pharmacodynamic summary

- Nelarabine is a water-soluble pro-drug of the deoxyguanosine analogue ara-G. Once within cells, ara-G is phosphorylated by deoxycytidine kinase and deoxyguanosine kinase and the subsequent accumulation of intracellular ara- GTP in leukaemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis resulting in cell death.
- Ara-G is markedly more toxic to T lymphoblasts than to blasts derived from other leukemic cell types, due to enhanced accumulation of ara-GTP in T cells compared with B cells and that deoxyguanosine inhibits proliferation to a greater extent in T-lymphoblasts than in mature T cells. Other mechanisms may contribute to the cytotoxic effects of nelarabine.
- A specific maximum-tolerated dose was not identified in the Phase 1 study in paediatric and adult patients with refractory haematologic malignancies. However, given that efficacy was

seen at all dose levels tested, a dose range (30 to 40 mg/kg) was recommended for initial phase 2 trials.

- Patients achieving a response to therapy with nelarabine accumulated significantly higher peak araGTP levels compared with non-responders in a study involving 19 patients with various haematologic malignancies. This relationship was also seen in a pilot study using a combination of nelarabine and fludarabine (Gandhi *et. al.,* 2001)
- Boddu et al (2022) provided preliminary evidence that continuous nelarabine infusion is associated with an acceptable safety profile with clinical responses observed even at low doses. This may potentially broaden use of nelarabine as monotherapy and in combination with other chemotherapy agents by reducing risks of CNS toxicities. However, this would require further evaluation in Phase 2/3 trials involving more patients.

Efficacy

The efficacy of nelarabine in paediatric and adult patients with R/R T-ALL and T-LBL following treatment with ≥ 2 chemotherapy regimens is considered to be adequately supported by literature findings.

Relapsed/refractory T-ALL/T-LBL

Nelarabine was approved by the U.S. FDA in 2005 and the EU- EMA in 2007 for the treatment of relapsing/refractory T-ALL/T-LBL in children and adults. The approval was based on two multi-centre, non-randomised, open-label, single-arm Phase 2 trials and limited to patients who had failed to respond to at least two prior chemotherapy regimens. The two Phase 2 studies which led to approval in USA and EU were published in Berg *et. al.,* 2005 and De Angelo, 2007:

- Berg *et. al.,* 2005[13]: This was a Phase 2 study in 121 patients with refractory T-cell malignancies. Of the 84 paediatric patients who received nelarabine at 650mg/m^2/d, an overall response rate (ORR) of 33% was reported; higher ORR was observed in patients with first relapse of T-ALL (55%) compared to those with ≥ 2 relapses (27%). Results from this study suggested a potential role for nelarabine in the treatment and/or prophylaxis of CNS leukaemia, as 8 of 22 patients who had positive CSF cytology prior to study entry converted to negative CSF cytology by day 7, prior to their scheduled intrathecal chemotherapy. Overall, this study confirmed efficacy/safety of nelarabine as monotherapy for children with R/R T-ALL and helped to refine the dose to 650mg/m^2/day for 5 days for children.
- De Angelo *et. al.,* 2007[14]: This Phase 2 study confirmed efficacy/safety of nelarabine monotherapy in 39 adult patients with R/R T-ALL or T-LBL. The dosing regimen, borrowed from an earlier phase I study to reduce neurotoxicity, was 1500 mg/m^2/d on days 1, 3 and 5 every 3 to 4 weeks. Additional rationale for an alternate day schedule was the observation that levels of ara-GTP in the circulating leukemia cells were maintained for more than 24 hours. In a heavily pretreated population, the ORR [(CR+CRi (complete remission with or without hematologic recovery) +PR (partial remission)] was 41%, including 31% CR+CRi. The ORR was 55% for patients in first salvage and 36% for those in ≥ 2nd salvage. 21% (4/19) of patients who had failed to respond to most recent induction treatment showed CR (complete remission) or CRi (incomplete remission) after nelarabine treatment. The median

[13] Berg SL, Blaney SM, Devidas M, Lampkin TA, Murgo A, Bernstein M, Billett A, Kurtzberg J, Reaman G, Gaynon P, Whitlock J, Krailo M, Harris MB; Children's Oncology Group. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol. 2005 May 20;23(15):3376-82. doi: 10.1200/JCO.2005.03.426. PMID: 15908649.

[14] DeAngelo DJ, Yu D, Johnson JL, Coutre SE, Stone RM, Stopeck AT, Gockerman JP, Mitchell BS, Appelbaum FR, Larson RA. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood. 2007 Jun 15;109(12):5136-42. doi: 10.1182/blood-2006-11-056754. Epub 2007 Mar 7. PMID: 17344466; PMCID: PMC1941786

disease-free survival (DFS) was 20 weeks. The median overall survival (OS) was 20 weeks, and the 1-year OS probability was 28%.

Since its initial approval, several studies have evaluated efficacy of nelarabine for its approved use in "R/R T-ALL/LBL whose disease had not responded to or relapsed following treatment with at least two chemotherapy regimens", including the following studies:

- Zwaan *et. al.,* 2017[15]: an ORR of 39% and 1-year survival rate of 35% (10/28 patients) was reported in a phase 4, open-label, observational study in 28 patients aged <21 years with T-ALL or T-LBL who had relapsed or were refractory following treatment with ≥ 2 chemotherapy regimens who received nelarabine 650mg/m^2. This was higher than that observed in the Phase 2 study (ORR of 27% and 1-year survival rate of 14% respectively) reported by Berg *et. al.*,[13]. However, results from this Phase 4 study are limited by the small sample size, open-label, observational uncontrolled study design, and risk of investigator bias as tumour responses were not confirmed independently.
- Gokbuget *et. al.,* 2011[16]: this was a prospective, open-label phase 2 trial conducted in Germany of nelarabine monotherapy in 126 adult patients with refractory T-ALL/T-LBL which reported an ORR of 46% with CR rate of 36%. Efficacy was seen in patients with limited treatment options as these patients were refractory to high dose chemotherapy regimens with 21% also having relapse after SCT. Furthermore, 42% of the patients with a PR after the first cycle achieved a CR after the second cycle (compared with only 14% achieving CR after failure). These results demonstrate potential benefits of administering a second nelarabine treatment cycle in all patients with partial remission and acceptable tolerability. Furthermore, the CR rate in patients with relapse after SCT was still 33%. However, none of the patients with T-LBL achieved a CR in this study. Nelarabine demonstrated impressive single-drug activity in highly resistant relapsed T-ALL and 80% of patients who achieved CR were transferred to SCT, and long-term relapse-free survival was achieved in one-third of these patients.
- Candoni *et. al.,* 2020[17]: this was a phase 4 study reporting an ORR of 50% and CR rate of 36% in 118 adult patients with R/R T-ALL/T-LBL with limited treatment options and a poor prognosis. 40% of patients following nelarabine salvage therapy could undergo SCT with an expected OS at 2 and 5 years of 46% and 38% respectively. However, results from this study are limited by the open-label, observational retrospective study design, and risk of investigator bias as tumour responses did not appear to be confirmed independently.

The results from these 2 latter studies[16,17] were consistent and provide evidence to support the potential use of a sequential program that includes nelarabine followed by SCT for adult patients with R/R T-ALL/T-LBL. Although neurological and haematological AEs were the most frequently reported AEs in both studies, deaths due to AEs were < 3% in both studies (mainly due to

[15] Zwaan CM, Kowalczyk J, Schmitt C, Bielorai B, Russo MW, Woessner M, Ranganathan S, Leverger G. Safety and efficacy of nelarabine in children and young adults with relapsed or refractory T-lineage acute lymphoblastic leukaemia or T-lineage lymphoblastic lymphoma: results of a phase 4 study. Br J Haematol. 2017 Oct;179(2):284-293. doi: 10.1111/bjh.14874. Epub 2017 Aug 2. PMID: 28771663.

[16] Gökbuget N, Basara N, Baurmann H, Beck J, Brüggemann M, Diedrich H, Güldenzoph B, Hartung G, Horst HA, Hüttmann A, Kobbe G, Naumann R, Ratei R, Reichle A, Serve H, Stelljes M, Viardot A, Wattad M, Hoelzer D. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. Blood. 2011 Sep 29;118(13):3504-11. doi: 10.1182/blood-2011-01-329441. Epub 2011 Jun 28. PMID: 21715318.-

[17] Candoni A, Lazzarotto D, Ferrara F, Curti A, Lussana F, Papayannidis C, Del Principe MI, Bonifacio M, Mosna F, Delia M, Minetto P, Gottardi M, Fracchiolla N, Mancini V, Forghieri F, Zappasodi P, Cerrano M, Vitale A, Audisio E, Trappolini S, Romani C, Defina M, Imbergamo S, Ciccone N, Santoro L, Cambò B, Iaccarino S, Dargenio M, Aprile L, Chiaretti S, Fanin R, Pizzolo G, Foà R. Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study. Am J Hematol. 2020 Dec;95(12):1466-1472. doi: 10.1002/ajh.25957. Epub 2020 Aug 31. PMID: 32777149.

infection complications). Further research into potential broader application of nelarabine in treatment of T-ALL/LBL was driven by following findings from studies evaluating nelarabine monotherapy: higher remission rates were observed with nelarabine in less heavily pre-treated patients, and that nelarabine did not cause significant myelosuppression and in absence of marrow disease could potentially be combined with other leukaemia drugs with non-overlapping toxicities.

The evidence from submitted studies for use of nelarabine in combination with other chemotherapy agents in R/R T-ALL/ LBL is summarised as follows:

- Preliminary evidence of efficacy/safety was provided for potential use of nelarabine in combination with fludarabine/etoposide[18] or VP/CPM[19] in paediatric and adolescent patients with R/R T-ALL or T-LBL. However, interpretation was limited by small patient numbers in these Phase 1/ 2 studies. Shimony *et. al.,*[20] reported a retrospective study involving 44 patients (adults and children) with CR rates of 40% and 62% following nelarabine monotherapy and combination therapy, respectively. Furthermore, 88% of the responders (21/24) were successfully bridged to allogeneic stem cell transplantation (alloSCT) resulting in overall median OS of 12.8 months. However, 2-year survival rates were significantly higher in those who received nelarabine combination compared to monotherapy (52.9% vs 8.2%) suggesting potential use of nelarabine combination therapy in the second line setting as a bridge to alloSCT.
- Evidence to support efficacy/safety of nelarabine in combination with other chemotherapy regimens in adult patients with R/R T-All or T-LBL was limited to small retrospective studies[21] and some case series [22,23].

Newly diagnosed T-ALL/T-LBL

Regarding the use of nelarabine in patients with newly diagnosed T-ALL/T-LBL:

- Dunsmore 2020: This pseudo-randomised Phase 3 study COG 0434 was the main basis providing evidence for efficacy/ safety of nelarabine as part of first line therapy for newly diagnosed patients (children and young adults aged <31 years) with T-ALL or T-LBL. Children and young adults (aged 1-31 years) with intermediate and high-risk T-ALL were randomised to receive nelarabine as part of consolidation therapy. Risk stratification was performed following a 28-day, prednisone-based, four-drug induction treatment. Patients

[18] Kumamoto T, Goto H, Ogawa C, Hori T, Deguchi T, Araki T, Saito AM, Manabe A, Horibe K, Toyoda H. FLEND (nelarabine, fludarabine, and etoposide) for relapsed T-cell acute lymphoblastic leukemia in children: a report from Japan Children's Cancer Group. Int J Hematol. 2020 Nov;112(5):720-724. doi: 10.1007/s12185-020-02962-2. Epub 2020 Aug 6. Erratum in: Int J Hematol. 2021 Feb;113(2):308-309. doi: 10.1007/s12185-020-03077-4. PMID: 32761462.

[19] Commander LA, Seif AE, Insogna IG, Rheingold SR. Salvage therapy with nelarabine, etoposide, and cyclophosphamide in relapsed/refractory paediatric T-cell lymphoblastic leukaemia and lymphoma. Br J Haematol. 2010 Aug;150(3):345-51. doi: 10.1111/j.1365-2141.2010.08236.x. Epub 2010 May 26. PMID: 20528871.

[20] Shimony S, Liu Y, Valtis YK, Paolino JD, Place AE, Brunner AM, Weeks LD, Silverman LB, Vrooman LM, Neuberg DS, Stone RM, DeAngelo DJ, Luskin MR. Nelarabine combination therapy for relapsed or refractory T-cell acute lymphoblastic lymphoma/leukemia. Blood Adv. 2023 Apr 11;7(7):1092-1102. doi: 10.1182/bloodadvances.2022008280. PMID: 36508268; PMCID: PMC10111357.

[21] Forcade E, Leguay T, Vey N, Baruchel A, Delaunay J, Robin M, Socié G, Dombret H, Peffault de Latour R, Raffoux E. Nelarabine for T cell acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation: an opportunity to improve survival. Biol Blood Marrow Transplant. 2013 Jul;19(7):1124-6. doi: 10.1016/j.bbmt.2013.04.010. Epub 2013 May 3. PMID: 23648236.

[22] Molle I, Petruskevicius I, Kamper P, d'Amore F. Salvage Therapy in Early Relapse of T-Lymphoblastic Leukemia/Lymphoma Using Daratumumab/Nelarabine Combination: Two Consecutive Cases. Case Rep Hematol. 2022 Jan 10;2022:9722787. doi: 10.1155/2022/9722787. PMID: 35047223; PMCID: PMC8763564.

[23] Luskin MR, Ganetsky A, Landsburg DJ, Loren AW, Porter DL, Nasta SD, Svoboda J, Luger SM, Frey NV. Nelarabine, cyclosphosphamide and etoposide for adults with relapsed T-cell acute lymphoblastic leukaemia and lymphoma. Br J Haematol. 2016 Jul;174(2):332-4. doi: 10.1111/bjh.13771. Epub 2015 Sep 25. PMID: 26403537.

who experienced induction failure were non-randomly assigned to HDMTX with nelarabine. Patients with low risk were not evaluated in this study. The 5-year DFS was significantly higher in the patients who received nelarabine (n=323) compared to those who did not (n=336): 88.2% vs 82.1% (p=0.029). Although the 5-year OS was numerically higher in the patients who received nelarabine compared to those who did not, the difference was not statistically significant (90.3% vs 87.9%, p=0.168). The best results were obtained among patients who were randomly assigned to receive nelarabine plus C-MTX. The addition of nelarabine to the HDMTX regimen in those who experienced induction failure improved DFS compared with HDMTX alone and decreased CNS relapse in both patients with and without CNS disease at diagnosis.

The incidence of CNS relapse was significantly lower for patients assigned to the nelarabine arms even though all patients received CRT. The decrease in incidence of CNS relapse was seen both in patients who were did and did not have CNS disease at diagnosis. The improvement in outcome may be explained by the activity of nelarabine in patients with higher-risk disease (high MRD and IF) and enhanced CNS prophylaxis. Overall, this pivotal study in newly diagnosed children and young adults (aged 1-31 years) with T-ALL supported the benefit of the addition of nelarabine to other chemotherapy in improving overall DFS; improvement in OS was not significant although it is acknowledged that the study was not powered to detect this.

- Dunsmore *et. al.,* 2012[24]: Supportive evidence was provided by the Phase 1 pilot study conducted in 88 in children/young adults (aged 1-22 years), with initial evidence to facilitate design and conduct of the larger Phase 3 study[25].
- In adult patients with newly diagnosed T-ALL/LBL, hyper-CVAD plus nelarabine showed some efficacy in the frontline setting with the ability to induce a high CR rate, durable remissions with no early mortality (Abaza, 2017; Jain, 2014). However, given the timing of the nelarabine later in the course of therapy, its contribution to CR rate is not clear. It is noted that the dose of nelarabine used in this setting was 650mg/m^2/day for 5 days (while proposed dose for adults in R/R T-All/LBL was 1500mg/m^2/day for 5 days). Overall, the addition of nelarabine to the hyper- CVAD regimen in adults (age range 19-78) with newly diagnosed T-ALL/LBL was not associated with improved outcomes. Despite the addition of nelarabine, the relapse rate remained high, was similar to previous studies with high mortality observed in relapsed patients.
- Comparison with historical results observed following hyper-CVAD treatment of adult patients with newly diagnosed T-ALL/LBL failed to show any difference in CR duration or OS following addition of nelarabine to hyper-CVAD. Furthermore, results of a Phase 2, randomised trial (UKALL14) reported no survival advantage with the addition of nelarabine to standard therapy among 144 adults aged 25-65 years (Rowntree *et. al.,* 2021). It is noted that this study was not provided in the submitted dossier.

The currently available evidence therefore does not support the use of nelarabine in adults with newly diagnosed T-ALL/LBL. Evidence to support use of nelarabine in newly diagnosed T-ALL/LBL in paediatric and young adults (<31 years) was also limited to consolidation therapy

[24] Dunsmore KP, Devidas M, Linda SB, Borowitz MJ, Winick N, Hunger SP, Carroll WL, Camitta BM. Pilot study of nelarabine in combination with intensive chemotherapy in high-risk T-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2012 Aug 1;30(22):2753-9. doi: 10.1200/JCO.2011.40.8724. Epub 2012 Jun 25. PMID: 22734022; PMCID: PMC3402886.

[25] Dunsmore KP, Winter SS, Devidas M, Wood BL, Esiashvili N, Chen Z, Eisenberg N, Briegel N, Hayashi RJ, Gastier-Foster JM, Carroll AJ, Heerema NA, Asselin BL, Rabin KR, Zweidler-Mckay PA, Raetz EA, Loh ML, Schultz KR, Winick NJ, Carroll WL, Hunger SP. Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia. J Clin Oncol. 2020 Oct 1;38(28):3282-3293. doi: 10.1200/JCO.20.00256. Epub 2020 Aug 19. PMID: 32813610; PMCID: PMC7526719.

with other chemotherapy agents (C-MTX) and only in those with intermediate/high risk patients (with risk stratification done following initial induction treatment).

Although some studies published since the initial approval of nelarabine in 2005 provide some evidence to support potential use of nelarabine combination therapy in the second line setting as a bridge to alloSCT, the evidence is limited to retrospective studies and case series.

The evaluation findings of the pooled and meta-analyses submitted in the dossier are noted (Kathpalia 2022; Kadia 2017; Cohen 2006); overall, most of the studies included in these reviews have been discussed in the studies above, with no meaningful additional information provided.

The clinical evaluator's conclusion on efficacy is as follows:

- Overall, the strongest evidence to support efficacy of nelarabine was limited to paediatric and adult patients with R/R T-ALL and T-LBL following treatment with $\geq$ 2 chemotherapy regimens which is similar to the currently approved indication in the USA and the EU.
- Following round 1 evaluation, the evidence for efficacy of nelarabine was considered to not be adequate for the broad indication proposed in this application: *"Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma."* The proposed wording does not indicate the patient population in which efficacy/safety of nelarabine was adequately demonstrated.
- Prior to round 2 evaluation, the sponsor changed the wording of the proposed indication based on the clinical evaluation's advice that *"there was strong evidence to support efficacy/ safety of nelarabine in "paediatric and adult patients with relapsing/refractory T-ALL/T-LBL especially those whose disease had not responded to or relapsed following treatment with at least two chemotherapy regimens" which is similar to currently approved indication in USA and EU".*
- Subsequently, the clinical evaluator concluded that the efficacy has been established for the currently proposed indication, with a favourable benefit risk profile for: *"Treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens."*

Safety

There were no studies conducted by the sponsor to provide evaluable safety data which was limited to that available in the submitted literature reports. Safety results were mainly discussed in terms of safety of nelarabine when used as monotherapy in patients with R/R T-ALL/T-LBL. One study conducted a retrospective analysis and reported differences in efficacy/safety when nelarabine was used as monotherapy or as combination therapy in children and adolescents with R/R T-ALL/T-LBL[26].

Safety in studies in patients with refractory/relapsing T-ALL/T-LBL include:

> Berg *et. al.*, 2005[13], De Angelo *et. al.* 2007[14], Gokbuget *et. al.*, 2011[16], Zwaan *et. al.*, 2017[15], Candoni *et. al.*, 2020[17], Shimony *et. al.*, 2022[20], Kuhlen *et. al.*, 2017[26], Forcade *et. al.*,

[26] Kuhlen M, Bleckmann K, Möricke A, Schrappe M, Vieth S, Escherich G, Bronsema A, Vonalt A, Queudeville M, Zwaan CM, Ebinger M, Debatin KM, Klingebiel T, Koscielniak E, Rossig C, Burkhardt B, Kolb R, Eckert C, Borkhardt A, von Stackelberg A, Chen-Santel C. Neurotoxic side effects in children with refractory or relapsed T-cell malignancies treated with nelarabine based therapy. Br J Haematol. 2017 Oct;179(2):272-283. doi: 10.1111/bjh.14877. Epub 2017 Aug 2. PMID: 28771662.

2013[21], Commander *et. al.*,, 2010[19], Kumamoto *et. al.*, 2020[18], Luskin *et. al.*, 2015[23], Amer-Sales *et. al.*,, 2020[27], Kathpalia *et. al.*, 2022[9],

Safety in patients with newly diagnosed T-ALL/T-LBL include:

Winter *et. al.*, 2015[28], Dunsmore *et. al.*, 2020[25], Dunsmore *et. al.*, 2012[24], Abaza *et. al.*, 2018[29], Jain *et. al.*, 2014[30].

Post-marketing experience: Many of the studies submitted in the current dossier were conducted after marketing approval for nelarabine was granted by the FDA (Arranon in 2005) and EU-EMA (Atriance in 2007).

The clinical evaluator's conclusion on safety is as follows:

- Safety data was provided by the studies which led to US-FDA and EU-EMA approvals in 2005 and 2007, respectively as well as studies conducted post-market authorisation
- The most common side effects reported in the literature include infection, febrile neutropenia, neutropenia, thrombocytopenia, anaemia, somnolence, peripheral neuropathy, hypoaesthesia, paraesthesia, dizziness, headache, dyspnoea, cough, diarrhoea, vomiting, constipation, nausea, myalgia, oedema, peripheral oedema, pyrexia, pain, tiredness, and weakness
- Neurologic toxicity was dose limiting for both paediatric and adult patients. Other severe toxicities included laboratory abnormalities in paediatric patients and gastrointestinal and pulmonary toxicities in adults
- It is noted that the proposed Australian PI was prepared based on AEs listed in the EMA approved SmPC. Safety results from the new studies evaluating nelarabine in different settings, stages of disease were not included in the Aus PI.

Risk management plan (RMP) evaluation

The current submission is based on literature and post-market adverse events reported to the regulators in the USA and Europe. The sponsor has submitted AUS-RMP version 1 (date and DLP not provided) in support of this application. With the s31 responses, the sponsor provided AUS-RMP version 2.0 (date 17 February 2023; DLP 1 February 2023).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in the following table:

[27] Amer-Salas N, González-Morcillo G, Rodríguez-Camacho JM, Cladera-Serra A. Nelarabine-associated myelopathy in a patient with acute lymphoblastic leukaemia: Case report. J Oncol Pharm Pract. 2021 Jan;27(1):244-249. doi: 10.1177/1078155220929747. Epub 2020 Jun 9. PMID: 32517638.

[28] Winter SS, Dunsmore KP, Devidas M, Eisenberg N, Asselin BL, Wood BL, Leonard Rn MS, Murphy J, Gastier-Foster JM, Carroll AJ, Heerema NA, Loh ML, Raetz EA, Winick NJ, Carroll WL, Hunger SP. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer. 2015 Jul;62(7):1176-83. doi: 10.1002/pbc.25470. Epub 2015 Mar 8. PMID: 25755211; PMCID: PMC4433576.

[29] Abaza Y, M Kantarjian H, Faderl S, Jabbour E, Jain N, Thomas D, Kadia T, Borthakur G, D Khoury J, Burger J, Wierda W, O'Brien S, Konopleva M, Ferrajoli A, Kebriaei P, Dabaja B, Kornblau S, Alvarado Y, Daver N, Pemmaraju N, Bose P, Thompson P, Al Azzawi H, Kelly M, Garris R, Jain P, Garcia-Manero G, Cortes J, Ravandi F. Hyper-CVAD plus nelarabine in newly diagnosed adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma. Am J Hematol. 2018 Jan;93(1):91-99. doi: 10.1002/ajh.24947. Epub 2017 Nov 3. PMID: 29047158.

[30] Jain P, Kantarjian H, Ravandi F, Thomas D, O'Brien S, Kadia T, Burger J, Borthakur G, Daver N, Jabbour E, Konopleva M, Cortes J, Pemmaraju N, Kelly MA, Cardenas-Turanzas M, Garris R, Faderl S. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. Leukemia. 2014 Apr;28(4):973-5. doi: 10.1038/leu.2013.312. Epub 2013 Oct 25. PMID: 24157581.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Neurotoxicity	P	–	P	–
Important potential risks	Risk in pregnancy (embryofetal toxicity)	P	–	P	–
Missing information	None	–	–	–	–

The summary of safety concerns is acceptable from an RMP perspective.

Only routine pharmacovigilance activities have been proposed. This approach is acceptable.

Risk-benefit analysis

Clinical evaluator's overall benefit-risk assessment

- Following round one evaluation, overall, the benefit-risk profile for nelarabine is not favourable for the proposed broad indication of: *"Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma."*
- The proposed wording does not indicate the patient population in which efficacy/safety of nelarabine was demonstrated.
- However, there is strong evidence to support efficacy/ safety of nelarabine in "paediatric and adult patients with relapsing/refractory T-ALL/T-LBL especially those whose disease had not responded to or relapsed following treatment with at least two chemotherapy regimens" which is similar to currently approved indication in USA and EU.
- During evaluation, the sponsor changed the proposed indication as recommended by the clinical evaluator. Hence, the benefit risk profile is now favourable for the modified proposed indication: *"Treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens."*

Clinical evaluator's recommendation

It is recommended that approval be granted for the following proposed indication:

"Treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens."

The sponsor has provided satisfactory response to all clinical questions from the first round evaluation and incorporated all recommended changes to the Australian PI.

T-ALL / T-LBL – disease and treatment

ALL and LBL are aggressive diseases that progress rapidly to a fatal outcome in the absence of effective therapy. LBL could be considered the lymphomatous variant of ALL in which extramedullary disease predominates in the absence of lesser involvement (<25% marrow

blasts) of the bone marrow compared to ALL. An important subset of ALL and LBL is the T-cell lineage form of the disease (i.e. T-ALL and T-LBL respectively), which is less frequent than B-cell lineage disease.

Current treatment for patients with T-LBL follows the same treatment strategy for T-ALL with comparable results. Patients newly diagnosed with ALL and LBL are typically treated with induction therapy (e.g. vincristine, prednisolone and anthracycline with/without asparaginase) followed by additional cycles of multi-agent chemotherapy regimen, with the aim of long term disease control. Approximately 25-30% of children experience relapse or are refractory to initial induction therapy resulting in a poor prognosis. Children who relapse within 6 months of completion of initial therapy have a 10-20% likelihood of long term survival when treated with chemotherapy alone, while those who relapse at over one year from completion of therapy have a 30-40% probability of long term survival. The cure rate of adults with T-ALL or T-LBL is lower than in children; after the first complete response, the majority of adult patients will eventually experience relapse.

Treatment in patients with relapsed or refractory disease is individualised based on the nature of response to prior therapy. Most patients with first relapse will receive multi-agent combination re-induction therapy which has demonstrated complete remission rates above 80% and range from 30-76% in clinical trials in children and adults respectively. Even if achieving a second remission, patients have a poor prognosis when treated with chemotherapy alone. Thus, these patients are recommended for reinduction chemotherapy followed by allo-SCT, or autologous transplantation. Long term event free survival rates up to 70% have been reported in children after BMT, lower for adults with relapsed ALL even with BMT.

The benefit of any new treatment agent must be assessed in the context that only CR or at least a significant reduction in leukaemic blasts would be of therapeutic benefit and that achievement of CR should be followed by additional chemotherapy and/or BMT when feasible.

Limited data exists for treatment agents for patients with T-ALL/T-LBL who have R/R disease following two or more prior induction attempts. However, it is noted that current NCCN guidelines recommend the following agents in this setting:

- Nelarabine +/- etoposide and cyclophosphamide
- Bortezomib + chemotherapy
- Daratumumab
- HiDAC – high dose cytarabine
- Mitoxantrone, etoposide and cytarabine
- Venetoclax + chemotherapy (e.g. decitabine, cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), methotrexate, and cytarabine and the steroid hormone dexamethasone (hyper-CVAD), nelarabine, mini-hyper-CVD (a lower intensity version of the hyper-CVAD regimen which omitting anthracycline and lowering the dose of the other agents).
- Augmented hyper-CVAD (The AHCVAD regimen uses the hyper-CVAD backbone with modifications: an intensified dose-schedule of vincristine, dexamethasone, pegaspargase with the addition of Rituximab for $CD20^+$ ALL patients).
- MOpAD (methotrexate, vincristine, PEG, dexamethasone)
- Clofarabine alone or in combo (n.b. this was registered in Australia in 2009 for paediatric patients with T-ALL (not including LBL) after at least 2 prior Rx regimen)

- Fludarabine based regimen – fludarabine, cytarabine, G-CSF +/- idarubicin; fludarabine, cytarabine, and mitoxantrone
- Cytarabine based regimen – high dose cytarabine, idarubicin, IT methotrexate
- Alkylator combination regimen – etoposide, ifosfamide, mitoxantrone

Benefits

Nelarabine has been registered and used for many years in the US and EU, and widely used under SAS system in Australia, for the treatment of patients with refractory/relapsing T-ALL/T-LBL.

The sponsor has not conducted any studies included in this submission. Evidence to support this application has been derived from clinical studies in the medical literature for nelarabine.

The use of nelarabine for the sponsor's currently proposed indication is supported by the literature; the sponsor has provided adequate evidence of effectiveness with several publications highlighting the efficacy of nelarabine for treatment of adult and paediatric patients with R/R T-ALL and T-LBL following treatment with $\geq$ 2 chemotherapy regimens.

Uncertainties of benefit

There is limited evidence (retrospective studies and case series/reports) to support the use of nelarabine for the following:

- as combination therapy for newly diagnosed T-ALL/LBL in paediatric patients (as consolidation therapy with other agents; Dunsmore 2020)
- as combination therapy for newly diagnosed T-ALL/LBL in adult patients
- in combination with other chemotherapy agents in R/R T-ALL/LBL

Lack of adequate information in elderly as insufficient numbers of patients aged 65 years of age and older have been treated with nelarabine to determine whether they respond differently than younger patients.

Risks

Nelarabine has been authorised in the US and EU for over 15 years and the safety concerns associated with its use are well established. The sponsor states that nelarabine has been available in Australia as different trade names supplied under the Special Access Scheme and no AEs have been reported to the TGA.

The following are commonly reported AEs for nelarabine:

- Neurotoxicity:
  - Reported in published papers and AE databases in the US and EU
  - Grade 3-4 neurotoxicity was the dose-limiting toxicity. Some manifestations were not reversible upon cessation of drug.
  - Somnolence, peripheral neuropathy, hypoaesthesia, paraesthesia, dizziness and headache are well recognised; reports of hallucinations, mood alterations, confusion, cognitive disturbances, impaired consciousness, facial nerve paralysis, paraplegia, encephalopathy, dysautonomia, retrobulbar neuritis and Guillain-Barre-like syndrome are noted

  - Grade 3-4 neurotoxicities in paediatric patients included headache, somnolence, hypoaesthesia, seizure and ataxia, and were usually reversible. Peripheral neuropathy was reported in one third of patients but only rarely at grade 3 or higher.

- Haematological toxicities:
  - Including neutropenia, febrile neutropenia, thrombocytopenia, anaemia
  - reported in published papers and AE databases in the US and Europe.
- Infections: There was a single additional report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult population. There have been reports of sometimes fatal opportunistic infections in patients receiving nelarabine therapy
- Fatigue
- Musculoskeletal weakness or pain
- Nausea/vomiting/diarrhoea
- Dyspnoea/cough
- Rash
- Biochemistry abnormalities including hypokalaemia, hyperglycaemia, hypocalcaemia, hyponatraemia and elevated AST

Uncertainties of risk

The number of patients in the clinical studies in the literature review provided was relatively small, limiting the ability to fully characterise rare AEs

Nelarabine has not been studied in patients with renal impairment. As nelarabine and 9-β-D-arabinofuranosylguanine (ara-G) are partially renally excreted, patients with renal impairment in particular must be closely monitored for toxicities when treated with nelarabine.

Nelarabine has not been studied in patients with hepatic impairment. These patients should be treated with caution.

Nelarabine was administered to a limited number of patients aged ≥ 65 years old.

Use in pregnancy: studies were not carried in pregnant persons. Nelarabine is considered unsuitable for use in pregnancy.

Conclusions

Overall, the benefit-risk assessment for nelarabine in the proposed population is considered to be favourable. The main uncertainty for both efficacy and safety in patients with refractory T-ALL/T-LBL arises from the limited data in the clinical trials evaluated due to small patient populations in these disease settings. Although nelarabine can cause serious toxicities (in particular, neurotoxicities which may be irreversible), the safety profile demonstrated is acceptable when considered in the context of the serious, life-threatening conditions being treated.

The delegate was supportive of the registration of nelarabine on the ARTG for the following indication:

> *"Nelarabine is indicated for the treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy*

regimens. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data."

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the delegate's overview, as well as the sponsor's response to these documents, provided the following advice:

1. Does ACM support the use of nelarabine for the proposed indication based on the available data and clinical experience with this agent in the Australian setting?

Based on the available data and clinical experience with the agent the ACM supported its use in the Australian setting. The ACM noted that T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma are rare and there are limited targeted treatment options currently available. Nelarabine offers a treatment with a different method of action that demonstrates adequate safety and efficacy.

The ACM noted the indication currently under consideration limits treatment with Nelarabine-Reach to patients whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Considering the literature provided in the dossier and the Australian context, the ACM was of the view that the indication should not be restricted to use following at least two chemotherapy regimens. In providing this view, the ACM noted that treatment with nelarabine can be considered as a bridge to stem cell transplantation and allowing its use in earlier treatment lines (i.e. at first relapse) can reduce the cumulative toxicity of multiple pre-transplantation treatments. The ACM also noted Nelarabine-Reach would be used by haematologists familiar with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma and removal of the lines of therapy from the indication will allow for individualised patient centred decision making.

The ACM noted that in the non-responsive and relapsed patient population there are small numbers of patients and as such was supportive of the following statement being included in a non-responsive and relapsed focussed indication:

Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.

The ACM discussed the paediatric setting and examined the larger Phase 3 randomised controlled trial in newly diagnosed patients aged 1 to 31 years (with most patients aged under 16 years). Although some study limitations were noted, the ACM commented on the favourable efficacy demonstrated by nelarabine in combination with multi-drug chemotherapy for this rare disease. Based on the evidence available to the ACM, the ACM was unsure why the indication (particularly for paediatric patients) was limited to those whose disease has not responded to or has relapsed. The ACM supported further exploration of use in newly diagnosed patients.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Nelarabine is indicated for the treatment of patients with relapsing /refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment.

Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.

Outcome

Based on a review of quality, safety, and efficacy data, the TGA decided to register Nelarabine-Reach for the above indication.

Specific conditions of registration applying to these goods

Nelarabine-Reach is to be included in the Black Triangle Scheme. The PI and CMI for Nelarabine Reach must include the black triangle symbol and mandatory accompanying text for five years.

The Black Triangle Scheme identifies new prescription medicines with a black triangle on the medicine information documents and serves as a visual reminder to encourage health practitioners and patients to report a problem or side effect associated with the medicine.

The Nelarabine-Reach Risk Management Plan (RMP) version 3.0 (date 17 February 2023; DLP 1 February 2023), included with submission PM-2023-00623-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of risk management plans is routine pharmacovigilance, which includes the submission of periodic safety update reports (PSURs).

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Nelarabine Reach which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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