Summary of the risk management plan for Atriance (nelarabine)

This is a summary of the risk management plan (RMP) for Atriance. The RMP details important risks of Atriance, how these risks can be minimized, and how more information will be obtained about Atriance's risks and uncertainties (missing information).

Atriance's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Atriance should be used.

This summary of the RMP for Atriance should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Atriance's RMP.

I. The medicine and what it is used for

Atriance is indicated for the treatment of patients with relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL).

Atriance contains nelarabine as the active substance and is administered intravenously.

Further information about the evaluation of Atriance's benefits can be found in Atriance's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/product-information/atriance-epar-product-information_en.pdf.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Atriance together with measures to minimize such risks and the proposed studies for learning more about Atriance's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Atriance is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Atriance are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Atriance. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Neurotoxicity[1]
Important potential risks	Risk in pregnancy (embryofetal toxicity)
Missing information	None

[1]Neurotoxicity: EU PASS Study PGA111081 revealed that the incidence and severity of neurological changes in subjects was consistent with previously reported clinical experience and current prescribing information. In addition, factors previously identified as potentially increasing the risk of subsequent neurological toxicity with nelarabine did not appear to predict toxicity in this small study.

In Study NLR506AUS02T, overall, the neurotoxicity of the augmented Berlin-Frankfurt-Münster regimen does not appear to have been significantly increased by the addition of nelarabine. The incidence and severity of neurotoxicity events observed in Study NLR506AUS02T is in line with previous experience with nelarabine in patients with refractory/resistant T-ALL.

II B: Summary of important risks

Important identified risks

Table 2 Important identified risk – neurotoxicity

Evidence for linking the risk to the medicine	Neurotoxicity was the primary dose limiting toxicity identified early in the development program during animal toxicity studies and clinical trials and is thus a recognized adverse effect of nelarabine therapy. Nelarabine caused histopathological changes to the central nervous system (white matter) vacuolation and degenerative changes in cerebrum, cerebellum and spinal cord of monkeys after treatment with nelarabine daily during 23 days, at exposures below the human therapeutic exposure. Neurotoxicity has been noted in pivotal trials, which includes peripheral neurological disorders (sensory and motor) 12-21%, hypoesthesia 6-17%,somnolence 7-23%, seizures 1-6%, amnesia 0-3%, paresthesia 4-15%, ataxia 2-9%, balance disorder 0-2%, tremor 4-5%, dizziness 0-21%, headache 15-17%, dysgeusia 0-3%. There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to GBS.

Risk factors and risk groups	As found during clinical trials, there was an apparent increased risk of neurological adverse events in patients previously treated with intrathecal chemotherapy or with craniospinal irradiation No other specific risk groups were identified during clinical trials.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects. **Additional risk minimization measures** Black box warning. Close monitoring for neurological reactions is strongly recommended, and nelarabine must be discontinued at the first sign of neurological reactions of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 2 or greater.

Important potential risk

Table 3 Important potential risk – risk in pregnancy (embryofetal toxicity)

Evidence for linking the risk to the medicine	Compared to controls, nelarabine caused increased incidences of fetal malformations, anomalies, and variations in rabbits when given at doses approximately 24% of the adult human dose on a mg/m^2 basis during the period of organogenesis.
Risk factors and risk groups	Embryos and/or fetus are at risk when exposed to nelarabine.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 Fertility, pregnancy and lactation. **Additional risk minimization measures** None

Missing information

There is no missing information.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

None.

II.C.2. Other studies in post-authorization development plan

There are no studies required for Atriance.