For use in India only
To be sold by retail on the prescription of Oncologist only

PRESCRIBING INFORMATION

WARNING: NEUROLOGIC ADVERSE REACTIONS

Severe neurologic adverse reactions have been reported with the use of Nelarabine. These adverse reactions have included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of adverse reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

Full recovery from these adverse reactions has not always occurred with cessation of therapy with Nelarabine. Monitor frequently for signs and symptoms of neurologic toxicity during treatment with Nelarabine. Discontinue Nelarabine for neurologic adverse reactions of NCI Common Toxicity Criteria for Adverse Events (CTCAE) Grade 2 or greater.

1. GENERIC NAME

Nelarabine Injection 250 mg/50 mL (5 mg/mL)

MSN
Nelabin
एम एस एन नेलाबिन

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nelarabine Injection 250 mg/50 mL (5 mg/mL)

Each mL contains Nelarabine 5 mg

3. DOSAGE FORM AND STRENGTH

Injection; 250 mg/50 mL (5 mg/mL)

4. CLINICAL PARTICULARS

4.1. Indication

Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

4.2. Posology and Method of Administration

Nelarabine must only be administered under the supervision of a physician experienced in the use of cytotoxic agents.

Posology

Complete blood counts including platelets must be monitored regularly.

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.

In clinical studies, the 650 mg/m^2 and 1,500 mg/m^2 dose have both been used in patients in the age range 16 to 21 years. Efficacy and safety were similar for both regimens. The prescribing physician should consider which regimen is appropriate when treating patients in this age range.

Limited clinical pharmacology data are available for patients below the age of 4 years.

Dose modification

Nelarabine must be discontinued at the first sign of neurological events of National Cancer Institute Common Terminology Criteria Adverse Event (NCI CTCAE) grade 2 or greater. Delaying subsequent dosing is an option for other toxicities, including haematological toxicity.

Method of Administration

Nelarabine is for intravenous use only and must not be diluted prior to administration. The appropriate dose of Nelarabine must be transferred into polyvinylchloride (PVC) or ethyl vinyl acetate (EVA) infusion bags or glass containers and administered intravenously as a two-hour infusion in adult patients and as a one-hour infusion in paediatric patients.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients used in the formulation

4.4. Special Warnings and Precautions for Use

Neurological Adverse Reactions

Severe neurological reactions have been reported with the use of Nelarabine. These reactions have included altered mental states including severe somnolence, confusion and coma, central nervous system effects including convulsions, ataxia and status epilepticus, and peripheral neuropathy including hypoesthesia ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré Syndrome. Neurotoxicity is the dose-limiting toxicity of Nelarabine. Full recovery from these reactions has not always occurred with cessation of Nelarabine. Therefore, close monitoring for neurological reactions is strongly recommended, and Nelarabine must be discontinued at the first sign of neurological reactions of NCI CTCAE Grade 2 or greater.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation are potentially at increased risk for neurological adverse and therefore concomitant intrathecal therapy and/or craniospinal irradiation is not recommended.

Vaccinations

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Hematologic Adverse Reactions

Leukopenia, thrombocytopenia, anaemia, and neutropenia, (including febrile neutropenia) have been associated with Nelarabine therapy. Complete blood counts including platelets must be monitored regularly.

Tumor Lysis Syndrome

Patients receiving Nelarabine are recommended to receive intravenous hydration according to standard medical practice for the management of hyperuricaemia in patients at risk of tumour lysis syndrome. For patients at risk of hyperuricaemia, the use of allopurinol should be considered.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, Nelarabine can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of nelarabine to pregnant rabbits during the period of organogenesis resulted in teratogenicity at maternal doses below the recommended human adult dose of 1,500 mg/m^2/day. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Nelarabine. Advise males with female partners of reproductive potential to use condoms during treatment with Nelarabine and for 3 months after the last dose.

Elderly

Clinical studies of Nelarabine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially age 65 years and older, appeared to be associated with increased rates of neurological adverse events.

Carcinogenicity and mutagenicity

Carcinogenicity testing of Nelarabine has not been performed. Nelarabine however, is known to be genotoxic to mammalian cells.

Sodium warning

This medicinal product contains 225.00 mg sodium per vial (50 ml), equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. 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. Concomitant administration may reduce the efficacy of Nelarabine and/or change the adverse event profile of either active substance.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no or limited amount of data from the use of Nelarabine in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk in humans is unknown, however, exposure during pregnancy will likely lead to anomalies and malformations of the foetus. Nelarabine should not be used during pregnancy unless clearly necessary. If a patient becomes pregnant during treatment with Nelarabine, they should be informed of the possible risk to the foetus.

Breast-feeding

It is unknown whether Nelarabine or its metabolites are excreted in human breast milk. A risk to the new born/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Nelarabine.

Contraception in males and females

Both sexually active men and women should use effective methods of contraception during treatment with Nelarabine. Men with partners who are pregnant or could become pregnant should use condoms during treatment with Nelarabine and for at least three months following cessation of treatment.

Fertility

The effect of Nelarabine on fertility in humans is unknown. Based on the pharmacological action of the compound, undesirable effects on fertility are possible. Family planning should be discussed with patients as appropriate.

Pediatric Use

The safety and effectiveness of Nelarabine for relapsed or refractory T-ALL and T-LBL has been established in pediatric patients age 1 year and older. The most frequent adverse reactions of any grade occurring on treatment in paediatric clinical study were hematologic laboratory abnormalities. Hematologic toxicity observed in the pediatric population was higher than that seen in the adult population. Nervous system adverse reactions have been reported for pediatric The incidence of nervous system adverse reactions was less in the pediatric population than that seen in adult patients with relapsed/refractory T-ALL/T-LBL. The safety profile was consistent with that seen in older patients in the paediatric clinical studies.

Due to lack of long-term follow up data, a determination of the impact of Nelarabine on the growth and pubertal development of pediatric patients cannot be made.

Geriatric Use

Clinical studies of Nelarabine did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially age 65 years and older, appeared to be associated with increased rates of neurologic adverse reactions. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

Renal Impairment

Nelarabine has not been studied in individuals with renal impairment. Ara-G clearance decreased as renal function decreased. Because the risk of adverse reactions to this drug may be greater in patients with moderate (CLCr 30 to 50 mL/min) or severe (CLCr less than 30 mL/min) renal impairment, these patients should be closely monitored for toxicities when treated with Nelarabine.

Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of Nelarabine has not been evaluated. Because the risk of adverse reactions to this drug may be greater in patients with severe hepatic impairment (total bilirubin greater than 3 times upper limit of normal), these patients should be closely monitored for toxicities when treated with Nelarabine.

4.7. Effects on Ability to Drive and Use Machines

Nelarabine has major influence on the ability to drive and use machines. Patients treated with Nelarabine are potentially at risk of suffering from somnolence during and for several days after treatment. Patients must be cautioned that somnolence can affect performance of skilled tasks, such as driving.

4.8. Undesirable Effects

Tabulated list of adverse reactions

The following convention has been utilised for the classification of frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Adverse reactions	**Adults**	**Children**
Infections and infestations		
Infection (including but not limited to; sepsis, bacteraemia, pneumonia, fungal infection)	Very common	Very common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour lysis syndrome (see also data from compassionate use programme and non-pivotal studies)	Common	N/A
Blood and lymphatic system disorders		
Febrile neutropenia	Very common	Common
Neutropenia	Very common	Very common
Leukopenia	Common	Very common
Thrombocytopenia	Very common	Very common
Anaemia	Very common	Very common
Metabolism and nutrition disorders		
Hypoglycaemia	N/A	Common
Hypocalcaemia	Common	Common
Hypomagnesaemia	Common	Common
Hypokalaemia	Common	Very common
Anorexia	Common	N/A
Psychiatric disorders		
Confusional state	Common	Common
Nervous system disorders		
Seizures (including convulsions, grand mal convulsions, status epilepticus)	Common	Common
Amnesia	Common	N/A
Somnolence	Very common	Common
Peripheral neurological disorders (sensory and motor)	Very common	Very common
Hypoesthesia	Very common	Common
Paraesthesia	Very common	Common
Ataxia	Common	Common
Balance disorder	Common	N/A
Tremor	Common	Common
Dizziness	Very common	N/A
Headache	Very common	Very common
Dysgeusia	Common	N/A
Eye disorder		
Blurred vision	Common	N/A
Vascular disorders		
Hypotension	Common	N/A
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	Common	N/A
Wheezing	Common	N/A
Dyspnoea	Very common	N/A
Cough	Very common	N/A
Gastrointestinal disorders		
Diarrhoea	Very common	Common
Stomatitis	Common	Common
Vomiting	Very common	Common
Abdominal pain	Common	N/A
Constipation	Very common	Common
Nausea	Very common	Common
Hepatobiliary disorders		
Hyperbilirubinaemia	Common	Common
Transaminases increased	N/A	Very common
Aspartate aminotransferase increased	Common	N/A
Musculoskeletal and connective tissue disorders		
Muscle weakness	Common	N/A
Myalgia	Very common	N/A
Arthralgia	Common	Common
Back pain	Common	N/A
Pain in extremity	Common	Common
Rhabdomyolysis, blood creatine phosphokinase increased	Rare: N/A	Rare: N/A
Renal and urinary disorders		
Blood creatinine increased	Common	Common
General disorders and administration site conditions		
Oedema	Very common	N/A
Gait abnormal	Common	N/A
Oedema peripheral	Very common	N/A
Pyrexia	Very common	Common
Pain	Very common	N/A
Fatigue	Very common	Common
Asthenia	Very common	Common

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +91- 40 38265227 (Direct line); +91 7331134745 (WhatsApp). By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose

No case of overdose has been reported.

Symptoms and signs

It is likely that Nelarabine overdose would result in severe neurotoxicity (possibly including paralysis, coma), myelosuppression and potentially death. At a dose of 2200 mg/m^2 given on days 1, 3 and 5 every 21 days, 2 patients developed a significant grade 3 ascending sensory neuropathy. MRI evaluations of the 2 patients demonstrated findings consistent with a demyelinating process in the cervical spine.

Treatment

There is no known antidote for Nelarabine overdose. Supportive care consistent with good clinical practice should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, purine analogues, ATC code: L01BB07.

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G. Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate metabolite. The monophosphate metabolite is subsequently converted to the active 5'- triphosphate form, ara-GTP. Accumulation of ara-GTP in leukaemic blasts allows for preferential incorporation of araGTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis. This results in cell death. Other mechanisms may contribute to the cytotoxic effects of Nelarabine. In vitro, T-cells are more sensitive than B-cells to the cytotoxic effects of Nelarabine.

5.2. Pharmacokinetic Properties

Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G. Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate metabolite. The monophosphate metabolite is subsequently converted to the active 5'- triphosphate from, ara-GTP. Accumulation of ara-GTP in leukaemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis. This results in cell death. Other mechanisms may contribute to the cytotoxic effects of Nelarabine. In vitro, T-cells are more sensitive than B-cells to the cytotoxic effects of Nelarabine.

In a cross-study analysis using data from four Phase I studies, the pharmacokinetics of Nelarabine and ara-G were characterized in patients aged less than 18 years and adult patients with refractory leukaemia or lymphoma.

Absorption

Adults

Plasma ara-G C_{max} values generally occurred at the end of the Nelarabine infusion and were generally higher than Nelarabine C_{max} values, suggesting rapid and extensive conversion of Nelarabine to ara-G. After infusion of 1,500 mg/m^2 Nelarabine over two hours in adult patients, mean (%CV) plasma Nelarabine C_{max} and AUC_{inf} values were 13.9 µM (81%) and 13.5 µM.h (56 %) respectively. Mean plasma ara-G C_{max} and AUC_{inf} values were 115 µM (16 %) and 571 µM.h (30 %), respectively. Intracellular C_{max} for ara-GTP appeared within 3 to 25 hours on day 1. Mean (%CV) intracellular ara-GTP C_{max} and AUC values were 95.6 µM (139 %) and 2214 µM.h (263 %) at this dose.

Paediatric patients

After infusion of 400 or 650 mg/m^2 Nelarabine over one hour in 6 paediatric patients, mean (%CV) plasma Nelarabine C_{max} and AUC_{inf} 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 C_{max} and AUC_{inf} values were 60.1 µM (17 %) and 212 µM.h (18 %), respectively.

Distribution

Nelarabine and ara-G are extensively distributed throughout the body based on combined Phase I pharmacokinetic data at Nelarabine doses of 104 to 2,900 mg/m^2. Specifically, for Nelarabine, mean (%CV) VSS values were 115 l/m^2 (159 %) and 89.4 l/m^2 (278 %) in adult and paediatric patients, respectively. For ara-G, mean VSS/F values were 44.8 l/m^2 (32 %) and 32.1 l/m2 (25 %) in adult and paediatric patients, respectively. Nelarabine and ara-G are not substantially bound to human plasma proteins (less than 25 %) in vitro, and binding is independent of Nelarabine or ara-G concentrations up to 600 µM. No accumulation of Nelarabine or ara-G was observed in plasma after Nelarabine administration on either a daily or a day 1, 3, 5 schedule. Intracellular ara-GTP concentrations in leukaemic blasts were quantifiable for a prolonged period after Nelarabine administration. Intracellular ara-GTP accumulated with repeated administration of Nelarabine. On the day 1, 3, and 5 schedule, C_{max} and $AUC_{(0-t)}$ values on day 3 were approximately 50 % and 30 %, respectively, greater than C_{max} and $AUC_{(0-t)}$ values on day 1.

Biotransformation

The principal route of metabolism for Nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition, some Nelarabine is hydrolysed to form methylguanine, which is Odemethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid.

Elimination

Nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and 3 hours, respectively. These findings were demonstrated in patients with refractory leukaemia or lymphoma given a dose of 1,500 mg/m^2 Nelarabine (adults) or a 650 mg/m^2 (paediatrics). Combined Phase 1 pharmacokinetic data at Nelarabine doses of 104 to 2,900 mg/m^2 indicate that mean (%CV) clearance (Cl) values for Nelarabine are 138 l/h/m^2 (104 %) and 125 l/h/m^2 (214 %) in adult and paediatric patients, respectively, on day 1 (n = 65 adults, n = 21 paediatric patients). The apparent clearance of ara-G (Cl/F) is comparable between the two groups [9.5 l/h/m^2 (35 %) in adult patients and 10.8 l/h/m^2 (36 %) in paediatric patients] on day 1. Nelarabine and ara-G are partially eliminated by the kidneys. In 28 adult patients, 24 hours after Nelarabine infusion on day 1, mean urinary excretion of Nelarabine and ara-G was 5.3 % and 23.2 % of the administered dose, respectively. Renal clearance averaged 9.0 l/h/m^2 (151 %) for Nelarabine and 2.6 l/h/m^2 (83 %) for ara-G in 21 adult patients. Because the time course of intracellular ara-GTP was prolonged, its elimination half-life could not be accurately estimated.

Paediatric population

Limited clinical pharmacology data are available for patients below the age of 4 years. Combined Phase 1 pharmacokinetic data at Nelarabine doses of 104 to 2,900 mg/m^2 indicate that the clearance (Cl) and Vss values for Nelarabine and ara-G are comparable between the two groups. Further data with respect to Nelarabine and ara-G pharmacokinetics in the paediatric population are provided in other subsections.

Gender

Gender has no effect on Nelarabine or ara-G plasma pharmacokinetics. Intracellular ara-GTP C_{max} and $AUC_{(0-t)}$ values at the same dose level were 2– to 3– fold greater on average in adult female than in adult male patients.

Race

The effect of race on Nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross study analysis, race had no apparent effect on Nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics.

Renal impairment

The pharmacokinetics of Nelarabine and ara-G have not been specifically studied in renally impaired or haemodialysed patients. Nelarabine is excreted by the kidney to a small extent (5 to 10 % of the administered dose). Ara-G is excreted by the kidney to a greater extent (20 to 30 % of the administered Nelarabine dose). Adults and children in clinical studies were categorized into the three groups according to renal impairment: normal with Clcr greater than 80 ml/min (n = 56), mild with Clcr equalling 50 to 80 ml/min (n = 12), and moderate with Clcr less than 50 ml/min (n = 2). The mean apparent clearance (Cl/F) of ara-G was about 7 % lower in patients with mild renal impairment than in patients with normal renal function (see section 4.2). No data are available to provide a dose advice for patients with Clcr less than 50 ml/min.

Elderly

Age has no effect on the pharmacokinetics of Nelarabine or ara-G. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance.

5.3 Pharmacodynamic Properties

Clinical efficacy and data

Adult clinical study in relapsed or refractory T-ALL and T-LBL

In an open-label study carried out by the Cancer and Leukaemia Group B and the Southwest Oncology Group, the safety and efficacy of Nelarabine were evaluated in 39 adults with T-cell acute lymphoblastic leukaemia (T-ALL) or lymphoblastic lymphoma (T-LBL). Twenty–eight of the 39 adults had relapsed or were refractory to at least two prior induction regimens and aged between 16 to 65 years of age (mean 34 years). Nelarabine at a dose of 1500 mg/m^2/day was administered intravenously over two hours on days 1, 3 and 5 of a 21-day cycle. Five of the 28 patients (18 %) [95 % CI: 6 %—37 %] treated with Nelarabine achieved a complete response (bone marrow blast counts ≤ 5 %, no other evidence of disease, and full recovery of peripheral blood counts). A total of 6 patients (21 %) [95 % CI: 8 %–41 %] achieved a complete response with or without haematological recovery. Time to complete response in both classifications of response ranged from 2.9 to 11.7 weeks. Duration of response (in both classifications of response (n=5) ranged between 15 and 195+ weeks. Median overall survival was 20.6 weeks [95 % CI: 10.4–36.4]. Survival at one year was 29 % [95 % CI: 12 %–45 %].

Paediatric clinical study in relapsed or refractory T-ALL and T-LBL

In an open-label, multicentre study carried out by Children's Oncology Group, Nelarabine was administered intravenously over 1 hour for 5 days to 151 patients ≤ 21 years of age, 149 of whom had relapsed or refractory T-cell acute lymphoblastic leukaemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients, 39 of whom had received two or more prior induction regimens and 31 whom had received one prior induction regimen, were treated with 650 mg/m^2/day of Nelarabine administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. Of the 39 patients who had received two or more prior induction regimens, 5 (13 %) [95 % CI: 4 %–27 %] achieved a complete response (bone marrow blast counts ≤ 5 %, no other evidence of disease, and full recovery of peripheral blood counts) and 9 (23 %) [95 % CI: 11 %–39 %] achieved complete responses with or without full haematological recovery. Duration of response in both classifications of response ranged between 4.7 and 36.4 weeks and median overall survival was 13.1 weeks [95 % CI: 8.7–17.4] and survival at one year was 14 % [95 % CI: 3 %–26 %]. Thirteen (42 %) of the 31 patients treated with one prior induction regimen achieved a complete response overall. Nine of these 31 patients failed to respond to prior induction (refractory patients). Four (44 %) of the nine refractory patients experienced a complete response to Nelarabine. This medicinal product has been authorised under "exceptional circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

6. NONCLINICAL PROPERTIES

6.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of Nelarabine has not been done. However, Nelarabine was mutagenic when tested in vitro in L5178Y/TK mouse lymphoma cells with and without metabolic activation. No studies have been conducted in animals to assess genotoxic potential or effects on fertility. The effect on human fertility is unknown.

7. PHARMACEUTICAL PARTICULARS

7.1. Incompatibilities

Not applicable.

7.2 Shelf-life

To be established.

7.3 Packing Information

50 ml Type I clear moulded vial with 20 mm bromobutyl serum rubber stopper and 20 mm aluminum flip off seals.

7.4 Storage and Handling Information

Store below 25^0 C.

The normal procedures for proper handling and disposal of cytotoxic anti-tumour medicinal products should be adopted, namely:

- Staff should be trained in how to handle and transfer the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during handling/transfer should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Any liquid waste from the preparation of the nelarabine solution for infusion may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

8. PATIENT COUNSELING INFORMATION

Hematologic Adverse Reactions

- Advise patients that leukopenia, thrombocytopenia, anemia, and neutropenia, including febrile neutropenia, have been associated with Nelarabine.
- Advise patients that complete blood counts, including platelets, will be monitored regularly during treatment.

Embryo-Fetal Toxicity

- Advise pregnant females of reproductive potential and males with female partners of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Nelarabine. Instruct females to inform their physician of a known or suspected pregnancy.
- Advise male patients with partners of reproductive potential to use condoms during treatment with Nelarabine and for 3 months after the last dose.

Tumor Lysis Syndrome

- Advise patients of the risk of tumor lysis syndrome.

Vaccinations

- Instruct patients not to receive live vaccines during treatment with Nelarabine.

Effects on Ability to Drive and Use Machines

• Patients receiving Nelarabine may experience somnolence during and for several days after treatment.
Instruct patients to not drive or engage in hazardous occupations or activities until somnolence has resolved.

Neurologic Adverse Reactions

- Instruct patients to contact their physician if they experience new or worsening symptoms of peripheral Neuropathy. These signs and symptoms include: tingling or numbness in fingers, hands, toes, or feet; difficulty with the fine motor coordination tasks such as buttoning clothing; unsteadiness while walking; weakness arising from a low chair; weakness in climbing stairs; increased tripping while walking over uneven surfaces.
- Advise patients of the risk of seizures. If a seizure occurs, instruct patients to promptly notify the physician administering Nelarabine.

Infection

• Instruct patients to promptly notify their physician if they develop fever or signs of infection while on Therapy.

Lactation

- Advise women not to breastfeed during treatment with Nelarabine.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division,
Unit II, Survey No. 1277 & 1319 to 1324,
Nandigama (Village and Mandal),
Rangareddy District, Pin Code: 509228,
Telangana, India.,

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Not Applicable

11. DATE OF REVISION

Jul 2023

C0307946-00

Dimensions: 270 x 550 mm
Font type: Arial Narrow & OCR-B 10 BT
Font size: 6 pt
Version No: 01

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Outer line not to be printed