NUCLOFAR CXXXXXX-XX

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NUCLOFAR
Clofarabine 1mg/ml Concentrate for Solution for Infusion

Label Claim:
Each ml of concentrate contains 1 mg of clofarabine .
Each 20 ml vial contains 20 mg of clofarabine.

Excipient with known effect:
Each 20 ml vial contains 180 mg of sodium chloride.

Each ml contains 1 mg of Clofarabine
For the full list of excipients, see Pharmaceutical Perticulars.

PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear colourless solution free from visible particulate matter.

CLINICAL PARTICULARS

Therapeutic indications
Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients (1 to 21 years old) who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis (see section Pharmacodynamic Properties).

Posology and method of administration

Recommended dose
Therapy must be initiated and supervised by a physician experienced in the management of patients with acute leukaemias.

Adults (including the elderly)
There are currently insufficient data to establish the safety and efficacy of clofarabine in adult patients (see section Pharmacokinetic Properties).

Paediatric patients

Children and adolescents (≥ 1 year old)
The recommended dose in monotherapy is 52 mg/m^2 of body surface area administered by intravenous infusion over 2 hours daily for 5 consecutive days. Body surface area must be calculated using the actual height and weight of the patient before the start of each cycle. Treatment cycles should be repeated every 2 to 6 weeks (from the starting day of the previous cycle) following recovery of normal haematopoiesis (i.e. ANC ≥ 0.75 × 109/l) and return to baseline organ function. A 25% dose reduction may be warranted in patients experiencing significant toxicities (see below). There is currently limited experience of patients receiving more than 3 treatment cycles (see section Special Warnings and Precautions for use).

The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles (see section Pharmacodynamic Properties). Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 2 treatment cycles should be assessed by the treating physician (see section Special Warnings and Precautions for Use).

Children weighing < 20 kg: An infusion time of > 2 hours should be considered to help reduce symptoms of anxiety and irritability, and to avoid unduly high maximum concentrations of clofarabine (see section Pharmacokinetic Properties).

Children < 1 year old: There are no data on the pharmacokinetics, safety or efficacy of clofarabine in infants. Therefore, a safe and effective dosage recommendation for patients (< 1 year old) has yet to be established.

Dose reduction for patients experiencing haematological toxicities
If the ANC does not recover by 6 weeks from the start of a treatment cycle, a bone marrow aspirate / biopsy should be performed to determine possible refractory disease. If persistent leukaemia is not evident, it is recommended that the dose for the next cycle be reduced by 25% of the previous dose following recovery of ANC to ≥ 0.75 × 109/l. Should patients experience an ANC < 0.5 × 109/l for more than 4 weeks from the start of the last cycle, it is recommended that the dose for the next cycle be reduced by 25%.

Dose reduction for patients experiencing non-haematological toxicities
Infectious events
If a patient develops a clinically significant infection, clofarabine treatment may be withheld until the infection is clinically controlled. At this time, treatment may be reinitiated at the full dose. In the event of a second clinically significant infection, clofarabine treatment should be withheld until the infection is clinically controlled and may be reinitiated at a 25% dose reduction.

Non-infectious events
If a patient experiences one or more severe toxicities (US National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade 3 toxicities excluding nausea and vomiting), treatment should be delayed until the toxicities resolve to baseline parameters or to the point where they are no longer severe and the potential benefit of continued treatment with clofarabine outweighs the risk of such continuation. It is then recommended that clofarabine be administered at a 25% dose reduction.

Should a patient experience the same severe toxicity on a second occasion, treatment should be delayed until the toxicity resolves to baseline parameters or to the point where it is no longer severe and the potential benefit of continued treatment with clofarabine outweighs the risk of such continuation. It is then recommended that clofarabine be administered at a further 25% dose reduction.

Any patient who experiences a severe toxicity on a third occasion, a severe toxicity that does not recover within 14 days (see above for exclusions), or a life-threatening or disabling toxicity (US NCI CTC Grade 4 toxicity) should be withdrawn from treatment with clofarabine (see section special warnings and precautions for use)

Special populations
Renal impairment: The limited data available indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see section Special Warnings and Precautions for Use and Pharmacokinetic Properties). Clofarabine is contraindicated in patients with severe renal insufficiency (see section Contraindications) and should be used with caution in patients with mild to moderate renal insufficiency (see section Special Warnings and Precautions for Use).

Patients with moderate renal impairment (creatinine clearance 30 - < 60 ml/min) require a 50% dose reduction (see section Pharmacokinetic Properties).

Hepatic impairment: There is no experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN) and the liver is a potential target organ for toxicity. Therefore, clofarabine is contraindicated in patients with severe hepatic impairment (see section Contraindications) and should be used with caution in patients with mild to moderate hepatic impairment (see section Special Warnings and Precautions for Use).

Method of administration
For instructions on dilution of the medicinal product before administration, see section Special Precautions for Disposal and Other Handling. The recommended dosage should be administered by intravenous infusion although it has been administered via a central venous catheter in ongoing clinical trials. Clofarabine must not be mixed with or concomitantly administered using the same intravenous line as other medicinal products (see section Incompatibilities).

Contraindications
Hypersensitivity to or to any of the excipients listed in section 6.1.
Use in patients with severe renal insufficiency or severe hepatic impairment.
Breast-feeding should be discontinued prior to, during and following treatment with Clofarabine.

Special warnings and precautions for use
Clofarabineis a potent antineoplastic agent with potentially significant haematological and non-haematological adverse reactions.

The following parameters should be closely monitored in patients undergoing treatment with clofarabine:
- Complete blood and platelet counts should be obtained at regular intervals, more frequently in patients who develop cytopaenias.
- Renal and hepatic function prior to, during active treatment and following therapy. Clofarabine should be discontinued immediately if substantial increases in creatinine or bilirubin are observed.
- Respiratory status, blood pressure, fluid balance and weight throughout and immediately after the 5 day administration period.

Suppression of bone marrow should be anticipated. This is usually reversible and appears to be dose- dependent. Severe bone marrow suppression, including neutropaenia, anaemia and thrombocytopaenia have been observed in patients treated with clofarabine. Haemorrhage, including cerebral, gastrointestinal and pulmonary haemorrhage, has been reported and may be fatal. The majority of the cases were associated with thrombocytopaenia.

In addition, at initiation of treatment, most patients in the clinical studies had haematological impairment as a manifestation of leukaemia. Because of the pre-existing immuno-compromised condition of these patients and prolonged neutropaenia that can result from treatment with clofarabine , patients are at increased risk for severe opportunistic infections, including severe sepsis, with potentially fatal outcomes. Patients should be monitored for signs and symptoms of infection and treated promptly.

Occurrences of enterocolitis, including neutropaenic colitis, caecitis, and *C. difficile* colitis, have been reported during treatment with clofarabine . This has occurred more frequently within 30 days of treatment, and in the setting of combination chemotherapy. Enterocolitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcome. Patients should be monitored for signs and symptoms of enterocolitis.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported. Clofarabine must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected.

Administration of clofarabine results in a rapid reduction in peripheral leukaemia cells. Patients undergoing treatment with clofarabine should be evaluated and monitored for signs and symptoms of tumour lysis syndrome and cytokine release (e.g. tachypnoea, tachycardia, hypotension, pulmonary oedema) that could develop into Systemic Inflammatory Response Syndrome (SIRS), capillary leak syndrome and/or organ dysfunction.
- Prophylactic administration of allopurinol should be considered if hyperuricemia (tumour lysis) is expected.
- Patients should receive intravenous fluids throughout the 5 day clofarabine administration period to reduce the effects of tumour lysis and other events.
- The use of prophylactic steroids (e.g., 100 mg/m^2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak.

Clofarabine should be discontinued immediately if patients show early signs or symptoms of SIRS, capillary leak syndrome or substantial organ dysfunction and appropriate supportive measures instituted. In addition, clofarabine treatment should be discontinued if the patient develops hypotension for any reason during the 5 days of administration. Further treatment with clofarabine, generally at a lower dose, can be considered when patients are stabilised and organ function has returned to baseline.

The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles. Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 2 treatment cycles should be assessed by the treating physician.

Patients with cardiac disease and those taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine.

There is no clinical study experience in paediatric patients with renal insufficiency (defined in clinical studies as serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys. Pharmacokinetic data indicate that clofarabine may accumulate in patients with decreased creatinine clearance. Therefore, clofarabine should be used with caution in patients with mild to moderate renal insufficiency. The safety profile of clofarabine has not been established in patients with severe renal impairment or patients receiving renal replacement therapy. The concomitant use of medicinal products that have been associated with renal toxicity and those eliminated by tubular secretion such as NSAIDs, amphotericin B, methotrexate, aminosides, organoplatines, foscarnet, pentamidine, cyclosporin, tacrolimus, acyclovir and valganciclovir, should be avoided particularly during the 5 day administration period; preference should be given to those medicinal products that are not known to be nephrotoxic.

It was observed that the frequency and severity of adverse reactions, in particular infection, myelosuppression (neutropenia) and hepatotoxicity, are increased when clofarabine is used in combination. In this regard, patients should be closely monitored when clofarabine is used in combined regimens.

Patients receiving may experience vomiting and diarrhoea; they should, therefore, be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, fainting spells, or decreased urine output. Prophylactic anti-emetic medicinal products should be considered.

There is no experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN) and the liver is a potential target organ for toxicity. Therefore, clofarabine should be used with caution in patients with mild to moderate hepatic impairment. The concomitant use of medicinal products that have been associated with hepatic toxicity should be avoided wherever possible.

If a patient experiences a hematologic toxicity of Grade 4 neutropaenia (ANC <0.5 x 10^9/l) lasting ≥4 weeks, then the dose should be reduced by 25% for the next cycle.

Any patient who experiences a severe non-hematologic toxicity (US NCI CTC Grade 3 toxicity) on a third occasion, a severe toxicity that does not recover within 14 days (excluding nausea/vomiting) or a life-threatening or disabling non-infectious non-hematologic toxicity (US NCI CTC Grade 4 toxicity) should be withdrawn from treatment with clofarabine.

Patients who have previously received a hematopoietic stem cell transplant (HSCT) may be at higher risk for hepatotoxicity suggestive of veno-occlusive disease (VOD) following treatment with clofarabine (40 mg/m^2) when used in combination with etoposide (100 mg/m^2) and cyclophosphamide (440 mg/m^2). In the post-marketing period, following treatment with clofarabine, serious hepatotoxic adverse reactions of VOD in paediatric and adult patients have been associated with a fatal outcome. Most patients received conditioning regimens that included busulfan, melphalan, and/or the combination of cyclophosphamide and total body irradiation. Severe hepatotoxic events have been reported in a Phase 1/2 combination study of in paediatric patients with relapsed or refractory acute leukaemia.

There are currently limited data on the safety and efficacy of clofarabine when administered for more than 3 treatment cycles.

Each vial of Clofarabine contains 180 mg of sodium chloride. This is equivalent to 3.08 mmol (or 70.77 mg) of sodium and should be taken into consideration for patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction
No formal interaction studies have been performed to date with . However, there are no known clinically significant interactions with other medicinal products or laboratory tests. Clofarabine is not detectably metabolised by the cytochrome P450 (CYP) enzyme system. Therefore, it is unlikely to interact with active substances which inhibit or induce cytochrome P450 enzymes. In addition, is unlikely to inhibit any of the major 5 human CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4) or to induce 2 of these isoforms (1A2 and 3A4) at the plasma concentrations achieved following intravenous infusion of 52 mg/m^2/day. As a result, it is not expected to affect the metabolism of active substances which are known substrates for these enzymes.

Clofarabine is predominately excreted via the kidneys. Thus, the concomitant use of medicinal products that have been associated with renal toxicity and those eliminated by tubular secretion such as NSAIDs, amphotericin B, methotrexate, aminosides, organoplatines, foscarnet, pentamidine, cyclosporin, tacrolimus, acyclovir and valganciclovir, should be avoided particularly during the 5 day administration period.

The liver is a potential target organ for toxicity. Thus, the concomitant use of medicinal products that have been associated with hepatic toxicity should be avoided wherever possible.

Patients taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine..

Fertility, pregnancy and lactation
Contraception in males and females
Females of childbearing potential and sexually active males must use effective methods of contraception during treatment.

Pregnancy
There are no data on the use of in pregnant women. Studies in animals have shown reproductive toxicity including teratogenicity. Clofarabine may cause serious birth defects when administered during pregnancy. Therefore, Clofarabine should not be used during pregnancy, especially not during the first trimester, unless clearly necessary (i.e. only if the potential benefit to the mother outweighs the risk to the foetus). If a patient becomes pregnant during treatment with , they should be informed of the possible hazard to the foetus.

Breast-feeding
It is unknown whether clofarabine or its metabolites are excreted in human breast milk. The excretion of in milk clofarabine has not been studied in animals. However, because of the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued prior to, during and following treatment with Clofarabine.

Fertility
Dose related toxicities on male reproductive organs have been observed in mice, rats and dogs, and toxicities on female reproductive organs have been observed in mice. As the effect of clofarabine treatment on human fertility is unknown, reproductive planning should be discussed with patients as appropriate.

Effects on ability to drive and use machines
No studies on the effects of clofarabine on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, light-headedness or fainting spells during treatment and told not to drive or operate machines in such circumstances.

Undesirable effects
Adverse reactions are listed by system organ class and frequency (very common, common, uncommon, rare and very rare) in the table below. Adverse reactions reported during the post-marketing period are also included in the table under the frequency category "not known" (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions considered to be related to clofarabine	
Infections and infestations	*Common:* Septic shock*, sepsis, bacteraemia, pneumonia, herpes zoster, herpes simplex, oral candidiasis *Frequency not known:* C. difficile colitis
Neoplasms benign and malignant (including cysts and polyps)	*Common:* Tumour lysis syndrome*
Blood and lymphatic system disorders	*Very common:* Febrile neutropaenia *Common:* Neutropaenia
Immune system disorders	*Common:* Hypersensitivity
Metabolism and nutrition disorders	*Common:* Anorexia, decreased appetite, dehydration Frequency not known: hyponatremia
Psychiatric disorders	*Very common:* Anxiety *Common:* Agitation, restlessness, mental status change
Nervous system disorders	*Very common:* Headache *Common:* Somnolence, peripheral neuropathy, paraesthesia, dizziness, tremor
Ear and labyrinth disorders	*Common:* Hypoacusis
Cardiac disorders	*Common:* Pericardial effusion*, tachycardia*
Vascular disorders	*Very common:* Flushing* *Common:* Hypotension*, capillary leak syndrome, haematoma
Respiratory, thoracic and mediastinal disorders	*Common:* Respiratory distress, epistaxis, dyspnoea, tachypnoea, cough
Gastrointestinal disorders	*Very common:* Vomiting, nausea, diarrhoea Common: Mouth haemorrhage, gingival bleeding, haematemesis, abdominal pain, stomatitis, upper abdominal pain, proctalgia, mouth ulceration *Frequency not known:* Pancreatitis elevations in serum amylase and lipase, enterocolitis, neutropaenic colitis, caecitis
Hepato-biliary disorders	*Common:* Hyperbilirubinaemia, jaundice, veno- occlusive disease, increases in alanine (ALT)* and aspartate (AST)* aminotransferases
General disorders and administration site conditions	*Very common:* Fatigue, pyrexia, mucosal inflammation *Common:* Multi-organ failure, systemic inflammatory response syndrome*, pain, chills, irritability, oedema, peripheral oedema, feeling hot, feeling abnormal
Skin and subcutaneous tissue disorders	*Very common:* Palmar-plantar erythrodysaesthesia syndrome, pruritus *Common:* Maculo-papular rash, petechiae, erythema, pruritic rash, skin exfoliation, generalised rash, alopecia, skin hyperpigmentation, generalised erythema, erythematous rash, dry skin, hyperhidrosis *Frequency not known:* Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders	*Common:* Pain in extremity, myalgia, bone pain, chest wall pain, arthralgia, neck and back pain
Renal and urinary disorders	*Common:* Haematuria*
Investigations	*Common:* Weight decreased
Injury, poisoning and procedural complications	*Common:* Contusion
* = see below**All adverse reactions occurring at least twice (i.e., 2 or more events (1.7%)) are included in this table	

Overdose
No case of overdose has been reported. However, possible symptoms of overdose are expected to include nausea, vomiting, diarrhoea and severe bone marrow suppression. To date, the highest daily dose administered to human beings is 70 mg/m2 for 5 consecutive days (2 paediatric ALL patients). The toxicities observed in these patients included vomiting, hyperbilirubinaemia, elevated transaminase levels and maculo-papular rash.

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No specific antidotal therapy exists. Immediate discontinuation of therapy, careful observation and initiation of appropriate supportive measures are recommended.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites,

ATC code: L01BB06.

Mechanism of action: Clofarabine is a purine nucleoside anti-metabolite. Its antitumour activity is believed to be due to 3 mechanisms:

- DNA polymerase inhibition resulting in termination of DNA chain elongation and/or DNA synthesis / repair.
- Ribonucleotide reductase inhibition with reduction of cellular deoxynucleotide triphosphate (dNTP) pools.
- Disruption of mitochondrial membrane integrity with the release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing lymphocytes.

Clofarabine must first diffuse or be transported into target cells where it is sequentially phosphorylated to the mono- and bi-phosphate by intracellular kinases, and then finally to the active conjugate, 5'-triphosphate. Clofarabine has high affinity for one of the activating phosphorylating enzymes, deoxycytidine kinase, which exceeds that of the natural substrate, deoxycytidine.

In addition, clofarabine possesses greater resistance to cellular degradation by adenosine deaminase and decreased susceptibility to phosphorolytic cleavage than other active substances in its class whilst the affinity of clofarabine triphosphate for DNA polymerase and ribonucleotide reductase is similar to or greater than that of deoxyadenosine triphosphate.

Pharmacodynamic effects: *In vitro* studies have demonstrated that clofarabine inhibits cell growth in and is cytotoxic to a variety of rapidly proliferating haematological and solid tumour cell lines. It was also active against quiescent lymphocytes and macrophages. In addition, clofarabine delayed tumour growth and, in some cases, caused tumour regression in an assortment of human and murine tumour xenografts implanted in mice.

Clinical efficacy and safety:
Clinical efficacy: To enable systematic evaluation of the responses seen in patients, an unblinded Independent Response Review Panel (IRRP) determined the following response rates based on definitions produced by the Children's Oncology Group:

CR = Complete Remission	Patients who met each of the following criteria: • No evidence of circulating blasts or extramedullary disease • An M1 bone marrow (≤ 5% blasts) • Recovery of peripheral counts (platelets 100 x 109/l and ANC 1.0 x 109/l)
CRp = Complete Remission in the Absence of Total Platelet Recovery	• Patients who met all of the criteria for a CR except for recovery of platelet counts to > 100 x 109/l
PR = Partial Remission	Patients who met each of the following criteria: • Complete disappearance of circulating blasts • An M2 bone marrow (5% and ≤ 25% blasts) and appearance of normal progenitor cells • An M1 marrow that did not qualify for CR or CRp
Overall Remission (OR) Rate	• (Number of patients with a CR + Number of patients with a CRp) ÷ Number of eligible patients who received Clofarabine
The safety and efficacy of clofarabine were evaluated in a phase I, open-label, non-comparative, dose-escalation study in 25 paediatric patients with relapsed or refractory leukaemia (17 ALL; 8 AML) who had failed standard therapy or for whom no other therapy existed. Dosing commenced at 11.25 with escalation to 15, 30, 40, 52 and 70 mg/m^2/day by intravenous infusion for 5 days every 2 to 6 weeks depending on toxicity and response. Nine of 17 ALL patients were treated with clofarabine 52 mg/m^2/day. Of the 17 ALL patients, 2 achieved a complete remission (12%; CR) and 2 a partial remission (12%; PR) at varying doses. Dose-limiting toxicities in this study were hyperbilirubinaemia, elevated transaminase levels and maculo-papular rash experienced at 70 mg/m^2/day.	

A multi-centre, phase II, open-label, non-comparative study of clofarabine was conducted to determine the overall remission (OR) rate in heavily pretreated patients (≤ 21 years old at initial diagnosis) with relapsed or refractory ALL defined using the French-American-British classification. The maximum tolerated dose identified in the phase I study described above of 52 mg/m^2/day clofarabine was administered by intravenous infusion for 5 consecutive days every 2 to 6 weeks. The table below summarises the key efficacy results for this study.

Patients with ALL must not have been eligible for therapy of higher curative potential and must have been in second or subsequent relapse and/or refractory i.e. failed to achieve remission after at least two prior regimens. Before enrolling in the trial, 58 of the 61 patients (95%) had received 2 to 4 different induction regimens and 18/61 (30%) of these patients had undergone at least 1 prior haematological stem cell transplant (HSCT). The median age of treated patients (37 males, 24 females) was 12 years old.

Administration of clofarabine resulted in a dramatic and rapid reduction in peripheral leukaemia cells in 31 of the 33 patients (94%) who had a measurable absolute blast count at baseline. The 12 patients who achieved an overall remission (CR + CRp) had a median survival time of 66.6 weeks as of the data collection cut-off date. Responses were seen in different immunophenotypes of ALL, including pre-B cell and T-cell. Although transplantation rate was not a study endpoint, 10/61 patients (16%) went on to receive a HSCT after treatment with clofarabine (3 after achieving a CR, 2 after a CRp, 3 after a PR, 1 patient that was considered a treatment failure by the IRRP and 1 that was considered not evaluable by the IRRP). Response durations are confounded in patients who received a HSCT.

Efficacy results from the pivotal study in patients (≤ 21 years old at initial diagnosis) with relapsed or refractory ALL after at least two prior regimens

Response category	ITT* patients (n = 61)	Median duration of remission (weeks) (95% CI)	Median time to progression (weeks)** (95% CI)	Median overall survival (weeks) (95% CI)
Overall remission (CR + CRp)	12 (20%)	32.0 (9.7 to 47.9)	38.2 (15.4 to 56.1)	69.5 (58.6 to -)
CR	7 (12%)	47.9 (6.1 to -)	56.1 (13.7 to -)	72.4 (66.6 to -)
CRp	5 (8%)	28.6 (4.6 to 38.3)	37.0 (9.1 to 42)	53.7 (9.1 to -)
PR	6 (10%)	11.0 (5.0 to -)	14.4 (7.0 to -)	33.0 (18.1 to -)
CR + CRp + PR	18 (30%)	21.5 (7.6 to 47.9)	28.7 (13.7 to 56.1)	66.6 (42.0 to -)
Treatment failure	33 (54%)	N/A	4.0 (3.4 to 5.1)	7.6 (6.7 to 12.6)
Not evaluable	10 (16%)	N/A		
All patients	61 (100%)	N/A	5.4 (4.0 to 6.1)	12.9 (7.9 to 18.1)

*ITT = intention to treat.
**Patients alive and in remission at the time of last follow up were censored at that time point for the analysis.

Individual duration remission and survival data for patients who achieved CR or CRp

Best Response	Time to OR (weeks)	Duration of Remission (weeks)	Overall Survival (weeks)
Patients who did not undergo transplant			
CR	5.7	4.3	66.6
CR	14.3	6.1	58.6
CR	8.3	47.9	66.6
CRp	4.6	4.6	9.1
CR	3.3	58.6	72.4
CRp	3.7	11.7	53.7
Patients who underwent transplant while in continued remission*			
CRp	8.4	11.6+	145.1+
CR	4.1	9.0+	111.9+
CRp	3.7	5.6+	42.0
CR	7.6	3.7+	96.3+
Patients who underwent transplant after alternative therapy or relapse*			
CRp	4.0	35.4	113.3+**
CR	4.0	9.7	89.4***

* Duration of remission censored at the time of transplant
** Patient received a transplant following alternate therapy
*** Patient received a transplant following relapse

Pharmacokinetic properties

Absorption and distribution
Multivariate analysis showed that the pharmacokinetics of clofarabine are weight dependent and although white blood cell (WBC) count was identified as having an impact on clofarabine pharmacokinetics, this did not appear sufficient to individualise a patient's dosage regimen based on their WBC count. Intravenous infusion of 52 mg/m^2 clofarabine produced equivalent exposure across a wide range of weights. However, C_{max} is inversely proportional to patient weight and, therefore, small children may have a higher C_{max} at the end of infusion than a typical 40 kg child given the same dose of clofarabine per m2. Accordingly, longer infusion times should be considered in children weighing < 20 kg.

Biotransformation and elimination
Clofarabine is eliminated by a combination of renal and non-renal excretion. After 24 hours, about 60% of the dose is excreted unchanged in the urine. Clofarabine clearance rates appear to be much higher than glomerular filtration rates suggesting filtration and tubular secretion as kidney elimination mechanisms. However, as clofarabine is not detectably metabolised by the cytochrome P450 (CYP) enzyme system, pathways of non-renal elimination currently remain unknown.
No apparent difference in pharmacokinetics was observed between patients with ALL or AML, or between males and females.
No relationship between clofarabine or clofarabine triphosphate exposure and either efficacy or toxicity has been established in this population.

Special populations

Adults (> 21 and < 65 years old)
There are currently insufficient data to establish the safety and efficacy of clofarabine in adult patients. However, the pharmacokinetics of clofarabine in adults with relapsed or refractory AML following administration of a single dose of 40 mg/m2 clofarabine by intravenous infusion over 1 hour were comparable to those described above in patients aged between 2 to 19 years old with relapsed or refractory ALL or AML following administration of 52 mg/m2 clofarabine by intravenous infusion over 2 hours for 5 consecutive days.

Elderly (≥ 65 years old)
There are currently insufficient data to establish the safety and efficacy of clofarabine in patients 65 years of age or older.

Renal impairment
To date, there are limited data on the pharmacokinetics of clofarabine in paediatric patients with decreased creatinine clearance.
Population pharmacokinetic data from adult and paediatric patients suggest that patients with stable moderate renal impairment (creatinine clearance 30 – < 60 ml/min) receiving a 50% dose reduction achieve similar clofarabine exposure to those with normal renal function receiving a standard dose.

Hepatic impairment
There is no experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN) and the liver is a potential target organ for toxicity.

PHARMACEUTICAL PARTICULARS

List of excipients
Sodium chloride Water for injection

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling.

Special precautions for storage
Do not store above 30^0 C.
Do not freeze.

The diluted concentrate is chemically and physically stable for 3 days at 2°C to 8°C and at room temperature (Upto 25°C). For microbiological point of view, it should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place under controlled and validated aseptic conditions.

Nature and contents of container
Type I glass vial with bromobutyl rubber stopper, and sealed with aluminium seal having polypropylene disc. The vials contain 20 ml concentrate for solution for infusion and are packaged in a box.
Presentation:
1 vial in one box

Instructions for Use
Clofarabine 1 mg/mL must be diluted prior to administration. Clofarabine is compatible with 0.9% Sodium Chloride.

Method of Administration
The recommended dosage should be administered by intravenous infusion although it has been administered via a central venous catheter in ongoing clinical trials. Clofarabine must not be mixed with or concomitantly administered using the same intravenous line as other medicinal products.

Special precautions for disposal and other handling
Clofarabine concentrate for solution for infusion must be diluted prior to administration. It should be filtered through a sterile 0.2 micrometre syringe filter and then diluted with sodium chloride 9 mg/ml (0.9%) intravenous infusion to produce a total volume according to the examples given in the table below. However, the final dilution volume may vary depending on the patient's clinical status and physician discretion. (If the use of a 0.2 micrometre syringe filter is not feasible, the concentrate should be pre-filtered with a 5 micrometre filter, diluted and then administered through a 0.22 micrometre in-line filter.)

Suggested dilution schedule based on the recommended dosage of 52 mg/m2/day clofarabine.		
Body surface area (m2)	Concentrate(ml)*	Total diluted volume
≤ 1.44	≤ 74.9	100 ml
1.45 to 2.40	75.4 to 124.8	150 ml
2.41 to 2.50	125.3 to 130.0	200 ml
*Each ml of concentrate contains 1 mg of clofarabine. Each 20 ml vial contains 20 mg of clofarabine. Therefore, for patients with a body surface area ≤ 0.38 m2, the partial contents of a single vial will be required to produce the recommended daily dosage of clofarabine. However, for patients with a body surface area > 0.38 m2, the contents of between 1 to 7 vials will be required to produce the recommended daily dosage of clofarabine.		

The diluted concentrate should be a clear, colourless solution. It should be visually inspected for particulate matter and discolouration prior to administration.
Clofarabine is for single use only. Any unused product must be discarded.
Procedures for proper handling of antineoplastic agents should be observed. Cytotoxic medicinal products should be handled with caution.
The use of disposable gloves and protective garments is recommended when handling Clofarabine. If the product comes into contact with eyes, skin or mucous membranes, rinse immediately with copious amounts of water.
Clofarabine should not be handled by pregnant women.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Controlled Medicine/ Ubat Terkawal
Keep out of the sight and reach of children.
Jauhi ubat dari kanak-kanak.

MEGA We care

Product Registration Holder:
MEGA LIFESCIENCES SDN. BHD.
B-28-02, The Ascent, Paradigm No. 1,
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Manufactured by:
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