EVOLTRA

1. NAME OF THE MEDICINAL PRODUCT

Evoltra 1 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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, which is equivalent to 3.6 mg of sodium per ml (0.2 mmol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, practically colourless solution with a pH of 4.5 to 7.5 and an osmolarity of 270 to 310 mOsm/l.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and who are about to undergo transplantation. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis (see section 5.1).

4.2 Posology and method of administration

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

Posology

Adult population (including the elderly)

There are currently insufficient data to establish the safety and efficacy of clofarabine in adult patients (see section 5.2).

Paediatric population

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 × 10^9/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 4.4).

The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles (see section 5.1). 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 4.4).

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 5.2).

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.

Patients with renal insufficiency: The limited data available indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see sections 4.4 and 5.2). Clofarabine is contraindicated in patients with severe renal insufficiency (see section 4.3) and should be used with caution in patients with mild to moderate renal insufficiency (see section 4.4).
Patients with moderate renal impairment (creatinine clearance 30 – <60 ml/min) require a 50% dose reduction (see section 5.2).

Patients with 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 4.3) and should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4).

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 × 10^9/l. Should patients experience an ANC < 0.5 × 10^9/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 4.4).

Method of administration

For instructions on filtration and dilution of the medicinal product before administration, see section 6.6. The recommended dosage should be administered by intravenous infusion although it has been administered via a central venous catheter in clinical trials. Evoltra must not be mixed with or concomitantly administered using the same intravenous line as other medicinal products (see section 6.2).

4.3 Contraindications

Hypersensitivity to clofarabine or to any of the excipients (see section 6.1).
Use in patients with severe renal insufficiency or severe hepatic impairment.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Evoltra is a potent antineoplastic agent with potentially significant haematological and non-haematological adverse reactions (see section 4.8).

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, liver enzymes and/or bilirubin are observed.
- Respiratory status, blood pressure, fluid balance and weight throughout and immediately after the 5 day clofarabine administration period.

Blood and lymphatic disorders

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 thrombocytopenia 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 (see section 4.8).
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 (see section 4.8). Patients should be monitored for signs and symptoms of enterocolitis.

Skin and subcutaneous tissue disorders

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), including fatal cases, have been reported (see section 4.8). Clofarabine must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected.

Neoplasms benign and malignant (including cysts and polyps) and Immune systems disorders

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 (see section 4.8).

- Prophylactic administration of allopurinol should be considered if hyperuricemia (tumour lysis) is expected.
- Patients should receive intravenous fluids throughout the five days of 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 patient is 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 (see section 5.1). 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.

Cardiac disorders

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 (see sections 4.5 and 4.8).

Renal and urinary disorders

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 (see section 5.2). Therefore, clofarabine should be used with caution in patients with mild to moderate renal insufficiency (see section 4.2 for dose adjustment).
The safety profile of clofarabine has not been established in patients with severe renal impairment or patients receiving renal replacement therapy (see section 4.3). 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 clofarabine administration period; preference should be given to those medicinal products that are not known to be nephrotoxic (see sections 4.5 and 4.8).
Renal failure or acute renal failure have been observed as a consequence of infections, sepsis and tumour lysis syndrome (see section 4.8). Patients should be monitored for renal toxicity and clofarabine should be discontinued as necessary.

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 clofarabine 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.

Hepato biliary disorders

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 (see sections 4.2 and 4.3). The concomitant use of medicinal products that have been associated with hepatic toxicity should be avoided wherever possible (see sections 4.5 and 4.8).
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 (see section 4.2).

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.
Cases of hepatitis and hepatic failure, including fatal outcomes, have been reported with clofarabine treatment (see section 4.8).
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 clofarabine in paediatric patients with relapsed or refractory acute leukemia.

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

Evoltra contains sodium

This medicinal product contains 72 mg sodium per vial, equivalent to 3.6% of the WHO recommended maximum daily intake for sodium.
The maximum daily dose of this product is equivalent to 23.4% of the WHO recommended maximum daily intake for sodium. Evoltra is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. 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, clofarabine 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 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 five days of clofarabine administration period (see sections 4.4, 4.8 and 5.2).

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 (see sections 4.4 and 4.8).

Patients taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine (see sections 4.4 and 4.8).

4.6 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 clofarabine in pregnant women. Studies in animals have shown reproductive toxicity including teratogenicity (see section 5.3). Clofarabine may cause serious birth defects when administered during pregnancy. Therefore, Evoltra 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 clofarabine, 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 clofarabine in milk 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 Evoltra (see section 4.3).

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 (see section 5.3). As the effect of clofarabine treatment on human fertility is unknown, reproductive planning should be discussed with patients as appropriate.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Nearly all patients (98%) experienced at least one adverse event considered by the study investigator to be related to clofarabine. Those most frequently reported were nausea (61% of patients), vomiting (59%), febrile neutropenia (35%), headache (24%), rash (21%), diarrhoea (20%), pruritus (20%) , pyrexia (19%), palmar-plantar erythrodysaesthesia syndrome (15%), fatigue (14%), anxiety (12%), mucosal inflammation (11%), and flushing (11%). Sixty-eight patients (59%) experienced at least one serious clofarabine-related adverse event. One patient discontinued treatment due to Grade 4 hyperbilirubinaemia considered as related to clofarabine after receiving 52 mg/m^2/day clofarabine. Three patients died of adverse events considered by the study investigator to be related to treatment with clofarabine: one patient died from respiratory distress, hepatocellular damage, and capillary leak syndrome; one patient from VRE sepsis and multi-organ failure; and one patient from septic shock and multi-organ failure.

Tabulated list of adverse reactions

The information provided is based on data generated from clinical trials in which 115 patients (> 1 and ≤ 21 years old) with either ALL or acute myeloid leukaemia (AML) received at least one dose of clofarabine at the recommended dose of 52 mg/m^2 daily x 5. Adverse reactions are listed by system organ class and 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) and very rare (<1/10,000)) 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.

Patients with advanced stages of ALL or AML may have confounding medical conditions that make causality of adverse events difficult to assess due to the variety of symptoms related to the underlying disease, its progression and the co-administration of numerous medicinal products.

Adverse reactions considered to be related to clofarabine reported at frequencies ≥ 1/1,000 (i.e. in > 1/115 patients) in clinical trials and post-marketing

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 neutropenia *Common:* Neutropenia
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, hematoma
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, hepatic failure *Uncommon:* hepatitis
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* *Common:* Renal failure, acute renal failure
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

Description of selected adverse reactions

Blood and lymphatic system disorders

The most frequent haematological laboratory abnormalities observed in patients treated with clofarabine were anaemia (83.3%; 95/114); leucopaenia (87.7%; 100/114); lymphopaenia (82.3%; 93/113), neutropaenia (63.7%; 72/113), and thrombocytopaenia (80.7%; 92/114).The majority of these events were of Grade ≥3.

During the post-marketing period prolonged cytopaenias (thrombocytopaenia, anaemia, neutropaenia and leukopaenia) and bone marrow failure have been reported. Bleeding events have been observed in the setting of thrombocytopaenia. Hemorrhage, including cerebral, gastrointestinal and pulmonaryhemorrhage, has been reported and may be associated with a fatal outcome (see section 4.4).

Vascular disorders

Sixty-four patients of 115 (55.7%) experienced at least one vascular disorders adverse event. Twenty-three patients out of 115 experienced a vascular disorder considered to be related to clofarabine, the most frequently reported being flushing (13 events; not serious) and hypotension (5 events; all of which were considered to be serious; see section 4.4). However, the majority of these hypotensive events were reported in patients who had confounding severe infections.

Cardiac disorders

Fifty percent of patients experienced at least one cardiac disorders adverse event. Eleven events in 115 patients were considered to be related to clofarabine, none of which were serious and the most frequently reported cardiac disorder was tachycardia (35%) (see section 4.4); 6.1% (7/115) patient's tachycardia were considered to be related to clofarabine. Most of the cardiac adverse events were reported in the first 2 cycles.

Pericardial effusion and pericarditis were reported as an adverse event in 9% (10/115) of patients. Three of these events were subsequently assessed as being related to clofarabine: pericardial effusion (2 events; 1 of which was serious) and pericarditis (1 event; not serious). In the majority of patients (8/10), the pericardial effusion and pericarditis were deemed to be asymptomatic and of little or no clinical significance on echocardiographic assessment. However, the pericardial effusion was clinically significant in 2 patients with some associated haemodynamic compromise.

Infections and infestations

Forty-eight percent of patients had one or more ongoing infections prior to receiving treatment with clofarabine. A total of 83% of patients experienced at least 1 infection after clofarabine treatment, including fungal, viral and bacterial infections (see section 4.4). Twenty-one (18.3%) events were considered to be related to clofarabine, of which catheter related infection (1 event), sepsis (2 events) and septic shock (2 events; 1 patient died (see above)) were considered to be serious.

During the post-marketing period, bacterial, fungal and viral infections have been reported and may be fatal. These infections may lead to septic shock, respiratory failure, renal failure, and/or multi-organ failure.

Renal and urinary disorders

Forty-one patients of 115 (35.7%) experienced at least one renal and urinary disorders adverse event. The most prevalent renal toxicity in paediatric patients was elevated creatinine. Grade 3 or 4 elevated creatinine occurred in 8% of patients. Nephrotoxic medicinal products, tumour lysis, and tumour lysis with hyperuricemia may contribute to renal toxicity (see sections 4.3 and 4.4). Haematuria was observed in 13% of patients overall. Four renal adverse events in 115 patients were considered to be related to clofarabine, none of which were serious; haematuria (3 events) and acute renal failure (1 event) (see sections 4.3 and 4.4).

Hepato-biliary disorders

The liver is a potential target organ for clofarabine toxicity and 25.2% of patients experienced at least one hepato-biliary disorders adverse event (see sections 4.3 and 4.4). Six events were considered to be related to clofarabine of which acute cholecystitis (1 event), cholelithiasis (1 event), hepatocellular damage (1 event; patient died (see above)) and hyperbilirubinaemia (1 event; the patient discontinued therapy (see above)) were considered to be serious. Two paediatric reports (1.7%) of Veno-Occlusive Disease (VOD) were considered related to study drug.

VOD cases reported during the post-marketing period in paediatric and adult patients have been associated with a fatal outcome (see section 4.4).

In addition, 50/113 patients receiving clofarabine had at least severely (at least US NCI CTC Grade 3) elevated ALT, 36/100 elevated AST and 15/114 elevated bilirubin levels. The majority of elevations in ALT and AST occurred within 10 days of clofarabine administration and returned to ≤ grade 2 within 15 days. Where follow-up data are available, the majority of bilirubin elevations returned to ≤ grade 2 within 10 days.

Systemic Inflammatory Response Syndrome (SIRS) or capillary leak syndrome

SIRS, capillary leak syndrome (signs and symptoms of cytokine release, e.g., tachypnea, tachycardia, hypotension, pulmonary oedema) were reported as an adverse event in 5% (6/115) of paediatric patients (5 ALL, 1 AML) (see section 4.4). Thirteen events of tumour lysis syndrome, capillary leak syndrome or SIRS have been reported; SIRS (2 events; both were considered to be serious), capillary leak syndrome (4 events; 3 of which were considered serious and related) and tumour lysis syndrome (7 events; 6 of which were considered related and 3 of which were serious).

Capillary leak syndrome cases reported during the post-marketing period have been associated with a fatal outcome (See section 4.4).

Gastrointestinal disorders

Occurrences of enterocolitis, including neutropaenic colitis, caecitis, and *C. difficile* colitis have been reported during treatment with clofarabine. Enterocolitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcome (see section 4.4).

Skin and subcutaneous disorders

Stevens - Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), including fatal cases, have been reported in patients who were receiving or had recently been treated with clofarabine. Other exfoliative conditions have also been reported.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms

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.

Management

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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 α 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, clofarabine 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 α 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 10^9/l and ANC ≥ 1.0 x 10^9/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 10^9/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/m²/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/m²/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/m²/day (2 ALL patients; see section 4.9).

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/m²/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		

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)
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[1]

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

5.2 Pharmacokinetic properties

Adsorption and distribution

Pharmacokinetics of clofarabine were studied in 40 patients aged between 2 to 19 years old with relapsed or refractory ALL or AML. Patients were enrolled into a single phase I (n = 12) or two phase II (n = 14 / n = 14) safety and efficacy studies, and received multiple doses of clofarabine by intravenous infusion (see section 5.1).

Pharmacokinetics in patients aged between 2 to 19 years old with relapsed or refractory ALL or AML following administration of multiple doses of clofarabine by intravenous infusion

Parameter	Estimates based on non-compartmental analysis (n = 14 / n = 14)	Estimates based on other analysis
Distribution:		
Volume of distribution (steady state)	172 l/m²	
Plasma protein binding		47.1%
Serum albumin		27.0%
Elimination:		
β half-life of clofarabine	5.2 hours	
Half-life of clofarabine triphosphate		> 24 hours
Systemic clearance	28.8 l/h/m²	
Renal clearance	10.8 l/h/m²	
Dose excreted in urine	57%	

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/m² 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 (see section 4.2).

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 patients (≥ 65 years old)

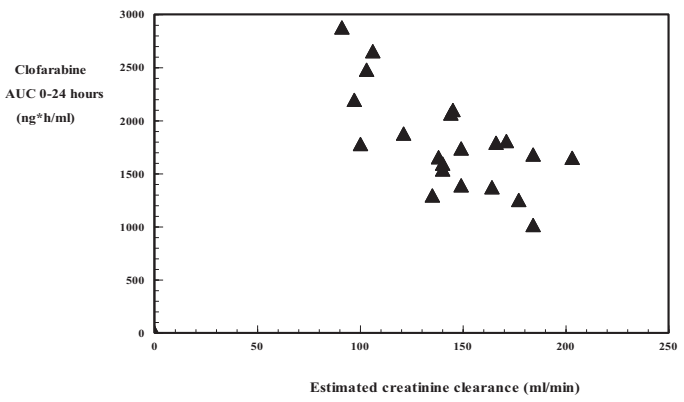
There are currently insufficient data to establish the safety and efficacy of clofarabine in patients 65 years of age or older.

Renal impairment

To date, there are limited data on the pharmacokinetics of clofarabine in paediatric patients with decreased creatinine clearance. However, these data indicate that clofarabine may accumulate in such patients (see figure below).

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.

Clofarabine $AUC_{0\text{-}24\ hours}$ by baseline estimated creatinine clearance in patients aged between 2 to 19 years old with relapsed or refractory ALL or AML (n = 11 / n = 12) following administration of multiple doses of clofarabine by intravenous infusion (creatinine clearance estimated using Schwartz formula)



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 (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Toxicology studies of clofarabine in mice, rats and dogs showed that rapidly proliferating tissues were the primary target organs of toxicity.

Cardiac effects were observed in rats consistent with cardiomyopathy and contributed to signs of cardiac failure after repeated cycles of treatment. The incidence of these toxicities was dependent on both the dose of clofarabine administered and the duration of treatment. They were reported at exposure levels (C_{max}) approximately 7 to 13 fold (after 3 or more dosing cycles) or 16 to 35 fold (after one or more dosing cycles) higher than clinical exposures. The minimal effects seen at lower doses suggest that there is a threshold for toxicities on the heart and nonlinear plasma pharmacokinetics in the rat may play a role in the observed effects. The potential risk for humans is unknown.

Glomerulonephropathy was reported in rats at exposure levels 3 to 5 fold higher than the clinical AUC after 6 dosing cycles of clofarabine. It was characterised by minor thickening of the glomerular basement membrane with only slight tubular damage and was not associated with changes in serum chemistry.

Hepatic effects were observed in rats following chronic administration of clofarabine. These likely represent the superimposition of degenerative and regenerative changes as a result of treatment cycles, and were not associated with changes in serum chemistry. Histological evidence of hepatic effects was seen in dogs following acute administration of high doses, but was also not accompanied by changes in serum chemistry.

Dose related toxicities on male reproductive organs were observed in mice, rats and dogs. These effects included bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells in rats at exaggerated exposure levels (150 mg/m²/day), and cell degeneration of the epididymis and degeneration of the seminiferous epithelium in dogs at clinically relevant exposure levels (≥ 7.5 mg/m²/day clofarabine).

Delayed ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at the only dose used of 225 mg/m²/day clofarabine.

Clofarabine was teratogenic in rats and rabbits. Increases in postimplantation loss, reduced foetal body weights and decreased litter sizes together with increases in the number of malformations (gross external, soft tissue) and skeletal alterations (including retarded ossification) were reported in rats receiving doses which produced approximately 2 to 3 fold the clinical exposure (54 mg/m²/day) and in rabbits receiving 12 mg/m²/day clofarabine. (There are no exposure data in rabbits.) The threshold for developmental toxicity was considered to be 6 mg/m²/day in rats and 1.2 mg/m²/day in rabbits. The no-observable effect level for maternal toxicity in rats was 18 mg/m²/day and in rabbits was more than 12 mg/m²/day. No fertility studies have been conducted.

Genotoxicity studies demonstrated that clofarabine was not mutagenic in the bacterial reverse mutation assay, but did induce clastogenic effects in the non-activated chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells and in the *in vivo* rat micronucleus assay.

No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Once prepared and diluted, Evoltra should be used straight away or within 24 hours if stored in a refrigerator (at 2 to 8°C).

6.4 Special precautions for storage

Store below 25°C. Do not freeze.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with bromobutyl rubber stopper, polypropylene flip-off cap and aluminium overseal. The vial contains 20 ml concentrate for solution for infusion and is packaged in a box. Each box contains 1, 3, 4, 10 or 20 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Special precautions for administration

Evoltra 1 mg/ml 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.

Instructions for handling

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 Evoltra. If the product comes into contact with eyes, skin or mucous membranes, rinse immediately with copious amounts of water.

Evoltra should not be handled by pregnant women.

Disposal

Evoltra is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

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Registration Number:
140 11 31946

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