AUSTRALIAN PRODUCT INFORMATION – EVOLTRA (CLOFARABINE)

1 NAME OF THE MEDICINE

Clofarabine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 20 mg of clofarabine. Each mL contains 1 mg of clofarabine. The pH of the solution ranges between 4.5 and 7.5 and it has an osmolarity of 270 to 310 mOsm/L.

Excipients of known effect:

Each 20 mL vial contains 180 mg of sodium chloride. This is equivalent to 3.8 mmol (or 70.77 mg) of sodium and should be taken into consideration for patients on a controlled sodium diet.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Concentrate for intravenous infusion.

Evoltra is a sterile, clear, practically colourless liquid which is free from foreign matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Evoltra is indicated for treatment of acute lymphocytic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens. This use is based on the induction of complete responses (see Section 5.1 Pharmacodynamic properties, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Paediatric patients: Administer the recommended paediatric dose of 52 mg/m^2 as an IV infusion over 2 hours daily for 5 consecutive days. Treatment cycles are repeated following recovery or return to baseline organ function, approximately every 2 to 6 weeks. The dosage

is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

In clinical trials with clofarabine in paediatric acute leukaemias, the median duration between cycles was 28 days (range of 12-55 days) [see Section 5.1 Pharmacodynamic properties, Clinical trials].

Provide IV infusion fluids throughout the 5 days of Evoltra administration to reduce the effects of tumour lysis and other adverse effects. Consider prophylactic anti-emetic medications as Evoltra is moderately emetogenic. The use of prophylactic steroids may be of benefit in preventing signs or symptoms of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnoea, and pulmonary oedema).

Most patients who respond to clofarabine do so within 1 to 2 treatment cycles (see Section 5.1 Pharmacodynamic properties, Clinical trials). The potential benefits and risks of continued therapy should be considered in those not responding after 2 cycles.

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 Pharmacokinetics).

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:

Administer subsequent cycles no sooner than 14 days from the starting day of the previous cycle provided the patient's ANC is $\geq 0.75 \times 10^9$/L.

If a patient experiences a Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting $\geq$ 4 weeks, reduce dose by 25% for the next cycle.

Dose reduction for patients experiencing non-haematological toxicities:

Withhold Evoltra if a patient develops a clinically significant infection, until the infection is clinically controlled and then restart 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.**

Withhold Evoltra if a Grade 3 non-infectious non-haematologic toxicity (excluding transient elevations in serum transaminases and/or serum bilirubin and/or nausea/vomiting that was controlled by antiemetic therapy) occurs. Re-institute Evoltra administration at a 25% dose reduction upon resolution or return to baseline.

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 Special warnings and precautions for use).

Evoltra administration should be stopped if the patient develops hypotension for any reason during the 5 days of administration. If hypotension is transient and resolves without pharmacological intervention, Evoltra treatment can be re-instituted generally with a 25% dose reduction.

Discontinue Evoltra administration if a patient shows early signs or symptoms of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnoea, and pulmonary edema) occur and provide appropriate supportive measures.

Discontinue Evoltra administration if substantial increases in creatinine or bilirubin are noted. Re-institute Evoltra when the patient is stable and organ function has returned to baseline, possibly with a 25% dose reduction. If hyperuricaemia is anticipated (tumour lysis), prophylactically administer allopurinol.

Patients with renal insufficiency: There is no experience in patients with renal insufficiency (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use). Close monitoring of renal function during the 5 days of Evoltra administration is advised [see Section 4.4 Special warnings and precautions for use]. Avoid drugs with known renal toxicity during the 5 days of Evoltra administration.

Patients with hepatic impairment: There is no experience in patients with hepatic impairment (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use). Close monitoring of hepatic function during the 5 days of Evoltra administration is advised [see Section 4.4 Special warnings and precautions for use]. Avoid concomitant use of medications known to induce hepatic toxicity.

Method of Administration

Evoltra contains no antimicrobial preservative. Product is for single use in one patient only. Discard any residue. See Section 6.6 Special precautions for disposal.

Evoltra must be diluted prior to administration (see below). The recommended dosage should be administered by intravenous infusion although it has been administered via a central venous catheter in ongoing clinical trials. Evoltra must not be mixed with or concomitantly administered using the same intravenous line as other medicinal products.

Evoltra 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 Table 1 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 sterile concentrate should be pre-filtered with a 5 micrometre filter, diluted and then administered through a 0.22 micrometre in-line filter).

Table 1: Suggested dilution schedule based on the recommended dosage of 52 mg/m^2/day clofarabine

Body surface area (m^2)	Sterile 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 m^2, 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 m^2, the contents of between 1 to 7 vials will be required to produce the recommended daily dosage of clofarabine.		

The diluted sterile concentrate should be a clear, colourless solution. Visually inspect for particulate matter and discolouration prior to administration.

For stability of the diluted sterile solution and associated information, refer to **STABILITY** section.

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.

Stability

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

4.3 CONTRAINDICATIONS

Clofarabine is contraindicated:

- In patients with hypersensitivity to clofarabine or to any of the excipients (see Section 6.1 List of Excipients);
- In patients with severe renal insufficiency or severe hepatic impairment;
- In breast-feeding women.

Breastfeeding should be discontinued prior to, during and following treatment with Evoltra (see Section 4.6 Fertility, pregnancy and lactation, Use in lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Evoltra should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Haematologic Toxicity

Obtain complete blood counts and platelet counts at regular intervals during Evoltra therapy.

Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Severe bone marrow suppression, including neutropenia, anaemia, and thrombocytopenia, has been observed in patients treated with Evoltra and may be prolonged. Haemorrhage, including cerebral, gastrointestinal and pulmonary haemorrhage, has been reported and may be fatal. The majority of cases were associated with thrombocytopenia (see Section 4.8 Adverse effects (Undesirable effects)). At initiation of treatment, most patients in the clinical studies had haematological impairment as a manifestation of leukaemia. Because of the pre-existing immunocompromised condition of these patients and prolonged neutropenia that can result from treatment with Evoltra, patients are at increased risk for severe opportunistic infections.

The most frequently reported haematologic adverse effects in paediatric patients have included febrile neutropenia (55%) and neutropenia (10%). One (1) report of grade 4 bone marrow depression, and 1 report of grade 4 thrombocytopenia were considered related to the study drug.

Infections

The use of Evoltra is likely to increase the risk of infection, including severe sepsis, as a result of bone marrow suppression. Infections may be associated with fatal outcomes.

At baseline, 48% of the paediatric patients had 1 or more concurrent infections. A total of 83% of patients experienced at least 1 infection after Evoltra treatment, including fungal, viral and bacterial infections. Twenty-one (18.3%) infection 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) were considered to be serious.

Hyperuricaemia (Tumour Lysis), and Capillary Leak Syndrome / SIRS

Administration of Evoltra results in a rapid reduction in peripheral leukaemia cells. Evaluate and monitor patients undergoing treatment with Evoltra for signs and symptoms of tumour lysis syndrome, as well as signs and symptoms of cytokine release (e.g., tachypnoea, tachycardia, hypotension, pulmonary oedema) that could develop into systemic inflammatory response syndrome (SIRS)/capillary leak syndrome and organ dysfunction. Early intervention is recommended. Provide IV infusion fluids throughout the five days of Evoltra administration to reduce the effects of tumour lysis and other adverse effects. Administer Allopurinol if hyperuricaemia (tumour lysis) is expected.

Discontinue Evoltra immediately in the event of clinically significant signs or symptoms of SIRS or capillary leak syndrome, either of which can be fatal, and consider use of steroids, diuretics, and albumin. Re-institute Evoltra when the patient is stable and organ function has returned to baseline, generally with a 25% dose reduction. The use of prophylactic steroids

(e.g., 100 mg/m^2 hydrocortisone on days 1 through 3) may be of benefit in preventing signs and symptoms of SIRS/Capillary Leak Syndrome or cytokine release.

Capillary leak syndrome or SIRS occurred in 6 paediatric patients overall (5 ALL, 1 AML). Several patients developed rapid onset of respiratory distress, hypotension, capillary leak (pleural and pericardial effusions), and multi-organ failure. Other concurrent medical conditions, including sepsis, may also have contributed to the incidence of capillary leak syndrome. In addition, prior therapies and/or disease progression may also make these patients more susceptible to capillary leak syndrome.

Renal failure/acute renal failure has been observed as a consequence of infections, sepsis and tumour lysis syndrome (see Section 4.8 Adverse effects (Undesirable effects)). Monitor patients for renal toxicity and interrupt or discontinue Evoltra as necessary.

Hepatobiliary Disorders

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). Veno-occlusive disease has also been observed in patients who had not received HSCT and were treated with clofarabine (52 mg/m^2) as the single chemotherapeutic agent. Severe hepatotoxic events have been reported in an ongoing Phase I / II combination study of clofarabine in paediatric patients with relapsed or refractory acute leukaemia. Cases of hepatitis and hepatic failure, including fatal incomes, have been reported with Evoltra treatment (see Section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for liver function and signs and symptoms of hepatitis and hepatic failure. Evoltra should be discontinued immediately if substantial increases in liver enzymes and/or bilirubin are observed.

Hepatobiliary toxicities were frequently observed in paediatric patients during treatment with Evoltra. Grade 3 or 4 elevated aspartate aminotransferase (AST) occurred in 36% of patients and grade 3 or 4 elevated alanine aminotransferase (ALT) occurred in 43% of patients. Grade 3 or 4 elevated bilirubin occurred in 13% of patients, with 2 events reported as grade 4 hyperbilirubinaemia (2%), one of which resulted in treatment discontinuation, one patient had multi-organ failure and died. One report (1%) of veno-occlusive disease (VOD) was considered related to the study drug.

For patients with follow-up data, elevations in AST and ALT were transient and typically ≤ 15 days duration. The majority of AST and ALT elevations occurred within 10 days of Evoltra 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. Eight patients had grade 3 or 4 elevations in serum bilirubin at the last time point measured, these patients died due to sepsis and/or multi-organ failure.

Renal and Urinary Disorders

The most prevalent renal toxicity in paediatric patients was elevated creatinine. Grade 3 or 4 elevated creatinine occurred in 8% of patients. Acute renal failure has been reported with Evoltra treatment (see Section 4.8 Adverse effects (Undesirable effects)). Nephrotoxic medications, tumour lysis, and tumour lysis with hyperuricaemia may contribute to renal

toxicity. Haematuria was observed in 13% of patients overall. This event likely reflects thrombocytopenia that is a pre-existing condition in these patients.

Vascular Disorders

Sixty-four patients of 115 (55.7%) experienced at least one vascular disorder adverse effect. 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). However, the majority of these hypotensive events were reported in patients who had confounding severe infections.

Gastrointestinal Disorders

Occurrences of enterocolitis including neutropenic colitis, cecitis and *C. difficile* colitis have been reported during treatment with Evoltra. Enterocolitis may lead to necrosis, perforation, haemorrhage or sepsis complications and may be associated with a fatal outcome (see Section 4.8 Adverse effects (Undesirable effects)). Patients should be monitored for liver function and signs and symptoms of enterocolitis.

Skin and Subcutaneous Disorders

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases have been reported (see Section 4.8 Adverse effects (Undesirable effects)). Evoltra must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected.

Cardiac Disorders

The most frequently reported cardiac disorder was tachycardia (35%), which was, however, already present in 35% of patients at study entry. Most of the cardiac adverse effects were reported in the first 2 cycles. Pericardial effusion was a finding in these patients on post-treatment studies, [9/115 (8%)]. The effusion was almost always minimal to small and in no cases had haemodynamic significance.

Use in Cardiac Disease

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 Section 4.5 Interactions with other medicines and other forms of interactions).

Dehydration/Hypotension

Patients receiving Evoltra may experience vomiting and diarrhea; 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, lightheadedness, fainting spells, or decreased urine output. Evoltra administration should be stopped if the patient develops hypotension for any reason during the 5 days of administration. If hypotension is transient and resolves without pharmacological intervention, Evoltra treatment can be re-instituted generally with a 25% dose reduction [see Section 4.2 Dose and method of administration].

Use in hepatic or renal impairment

Evoltra has not been studied in patients with hepatic or renal dysfunction. In severe dysfunction, Evoltra is contraindicated. In mild to moderate dysfunction, Evoltra should be used with the greatest caution [see Section 4.2 Dose and method of administration].

Use in adults (> 21 and < 65 years old)

Safety and effectiveness have not been established in adults.

Use in the elderly (≥ 65 years old)

There are currently insufficient data to establish the safety and efficacy of clofarabine in elderly patients.

Paediatric use (> 1 and ≤ 21 years old)

The safety and efficacy have been established in children.

Effects on laboratory tests

There are no known clinically significant interactions of Evoltra with laboratory tests. No formal drug/laboratory test interaction studies have been conducted with Evoltra.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the *in vitro* studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. Clofarabine did not significantly inhibit the activity of CYP3A4, CYP2D6, CYP2C9, CYP2C19 and CYP1A2 at clinically relevant concentrations *in vitro*. Weak induction of CYP1A2 and CYP3A4 occurred in human hepatocytes *in vitro* at clofarabine concentrations of 0.5-12 μg/mL, which was slightly higher than the clinical C_{max}.

Clofarabine is predominately excreted via the kidneys. Hence, the concomitant use of medicinal products that have been associated with renal toxicity and those eliminated by tubular secretion should be avoided particularly during the 5 day clofarabine administration period.

Since the liver is a potential target organ for toxicity, 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.

There are no known clinically significant interactions of Evoltra with other medications or laboratory tests. No formal drug/laboratory test interaction studies have been conducted with Evoltra.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were reported in male mice receiving intraperitoneal (IP) doses of 3 mg/kg/day (9 mg/m^2/day, approximately 17% of clinical recommended dose on an AUC basis). The testes of rats receiving 25 mg/kg/day (approximately 5 times the recommended clinical dose on an AUC basis) in a 6-month IV study had bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells. In a 6-month IV dog study, cell degeneration of the epididymis and degeneration of the seminiferous epithelium in the testes were observed in dogs receiving 0.375 mg/kg/day (approximately 30% of the clinical recommended dose on an AUC basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day IP (225 mg/m^2/day, approximately 4-fold of recommended human dose on a mg/m^2 basis), the only dose administered to female mice. Atrophy of the ovaries, uterus and vagina occurred in female rats receiving 12.5 g/kg/day (approximately 4 times the recommended clinical dose on an AUC basis). As the effect of clofarabine treatment on human fertility is unknown, reproductive planning should be discussed with patients as appropriate.

Use in pregnancy

Category D[1]

[1]Drugs which have caused, are expected to have caused or may be expected to cause, an increased risk of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Evoltra (clofarabine) may cause foetal harm when administered to a pregnant woman.

Clofarabine was teratogenic in rats and rabbits. Developmental toxicity (reduced foetal body weight and increased post-implantation loss) and increased incidences of malformations and variations (gross external, soft tissue, skeletal and retarded ossification) were observed in rats receiving 1 mg/kg/day (approximately 40% of the recommended clinical dose on an extrapolated AUC basis), and in rabbits receiving 1 mg/kg/day (12 mg/m^2/day; approximately 23% of the recommended clinical dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using clofarabine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

Due to the genotoxic risk of clofarabine women of childbearing potential must use effective methods of contraception during treatment with clofarabine and for 6 months following completion of treatment.

Men should use effective methods of contraception and be advised to not father a child while receiving clofarabine, and for 3 months following completion of treatment.

Use in lactation

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. Because of the potential for tumorigenicity shown for clofarabine in animal studies and the potential for serious adverse effects, women treated with clofarabine should not nurse. Female patients should be advised to avoid breast-feeding during treatment with Evoltra and for at least 2 weeks after the last dose (see Section 4.3 Contraindications).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

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.

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

Nearly all patients (98%) experienced at least one adverse effect 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 effect. One patient discontinued treatment due to grade 4 hyperbilirubinaemia considered as related to clofarabine after receiving 52 mg/m^2/day clofarabine. 3 patients died of adverse effects 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.

Table 2 lists adverse effects by System Organ Class, including severe or life-threatening events (NCI CTC grade 3 or grade 4), reported in ≥ 1% of the 115 patients in the 52 mg/m^2/day dose group (pooled analysis of paediatric patients with ALL and AML).

Table 3 lists the incidence of treatment emergent laboratory abnormalities after Evoltra administration at 52 mg/m^2 among paediatric patients with ALL and AML (n=115).

Table 2: Adverse effects considered to be related to clofarabine reported at frequencies ≥ /100 (i.e. in > 1/115 patients) in clinical trials
(Very common = ≥ 1/10; Common = ≥ 1/100 to < 1/10)

Blood and the lymphatic system disorders	*Very common:* Febrile neutropenia *Common:* Neutropenia
Cardiac disorders	*Common:* Pericardial effusion*, tachycardia*
Ear and labyrinth disorders	*Common*: Hypoacusis
Gastrointestinal disorders	*Very common:* Vomiting, diarrhoea, nausea *Common:* Haematemesis, mouth haemorrhage, abdominal pain, abdominal pain upper, gingival bleeding, mouth ulceration, proctalgia, stomatitis
General disorders and administration site conditions	*Very common:* Pyrexia, mucosal inflammation, fatigue *Common:* Multi-organ failure, pain, oedema, peripheral oedema, feeling hot, feeling abnormal, chills, systemic inflammatory response syndrome*, irritability
Hepato-biliary disorders	*Common:* Jaundice, veno-occlusive disease, alanine aminotransferase increased (ALT)* and aspartate (AST)* aminotransferase increased, hyperbilirubinaemia
Immune system disorders	*Common:* Hypersensitivity
Infections and infestations	*Common:* Septic shock*, sepsis, bacteraemia, pneumonia, herpes zoster, herpes simplex, oral candidiasis
Injury, poisoning and procedural complications	*Common:* Contusion
Investigations	*Common:* Weight decreased
Metabolism and nutrition disorders	*Common:* Dehydration, anorexia, decreased appetite
Musculoskeletal, connective tissue and bone disorders	*Common:* Musculoskeletal chest pain, bone pain, neck pain, back pain, pain in extremity, myalgia, arthralgia
Neoplasms benign and malignant (including cysts and polyps)	*Common:* Tumour lysis syndrome*
Nervous system disorders	*Very common:* Headache *Common:* Neuropathy peripheral, paraesthesia, somnolence, dizziness, tremor
Psychiatric disorders	*Very common:* Anxiety *Common:* Agitation, restlessness, mental status changes
Renal and urinary disorders	*Common:* Haematuria*
Respiratory, thoracic and mediastinal disorders	*Common:* Tachypnoea, epistaxis, dyspnoea, cough, respiratory distress
Skin and subcutaneous tissue disorders	*Very common:* Pruritus, palmar-plantar erythrodysaesthesia syndrome *Common:* Petechiae, rash generalised, erythema, rash pruritic, alopecia, rash maculo-papular, generalised erythema, rash erythematous, skin hyperpigmentation, dry skin, hyperhidrosis, skin exfoliation
Vascular disorders	*Very common:* Flushing* *Common:* Hypotension*, haematoma, capillary leak syndrome

* see Section 4.4 Special warnings and precautions for use
Note all adverse effects occurring at least twice (i.e., 2 or more events (1.7%)) are included in this table.

Uncommon Effects

Gastrointestinal Disorders: Pancreatitis, serum amylase and lipase elevation

Skin Disorders: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)

Eye disorders: Ocular icterus

Table 3: Incidence of Treatment Emergent Laboratory Abnormalities After Evoltra Administration

Parameter	Any Grade	Grade 3 or higher
Haematology		
Anaemia (N=114)	95 (83.3%)	86 (75.4%)
Leukopenia (N=114)	100 (87.7%)	100 (87.7%)
Lymphopenia (N=113)	93 (82.3%)	93 (82.3%)
Neutropenia (N=113)	72 (63.7%)	72 (63.7%)
Thrombocytopenia (N=114)	92 (80.7%)	91 (79.8%)
Blood creatinine increased (N=115)	57 (49.5%)	9 (7.8%)
Aspartate aminotransferase increased (N=100)	74 (74.0%)	36 (36.0%)
Alanine aminotransferase increased (N=113)	91 (80.5%)	49 (43.4%)
Blood bilirubin increased (N=114)	51 (44.7%)	15 (13.2%)

Post-marketing Experience

The following adverse effects have been identified during post approval use of Evoltra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal connection to Evoltra.

- Blood and lymphatic system disorders: Bone marrow failure and prolonged pancytopenia (thrombocytopenia, anaemia, neutropenia and lymphopenia) may occur. Bleeding events have been observed in the setting of thrombocytopenia. Haemorrhage, including cerebral and pulmonary haemorrhage, has been reported and may be fatal.

- Gastrointestinal disorders: Gastrointestinal haemorrhage has been observed and may be associated with a fatal outcome. Enterocolitis, including neutropenic colitis, cecitis and *C. difficile* colitis may lead to necrosis, perforation or sepsis complications and may be associated with fatal outcomes.

- Hepatobiliary disorders: Serious hepatotoxic events of venoocclusive disease have been reported and may be fatal in patients who had previous HSCT and who received conditioning regimens that included busulfan, melphalan, and/or the combination of cyclophosphamide and total body irradiation. Cases of hepatitis and hepatic failure have been reported, including fatal outcomes (see Section 4.4 Special warnings and precautions for use).

- Metabolism and nutrition disorders: hyponatremia

- Skin and subcutaneous disorders: Occurrences of 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 Evoltra and other medications (e.g. allopurinol or antibiotics) known to cause these syndromes. Other exfoliative conditions have also been reported (see Section 4.4 Special warnings and precautions for use).

- Vascular Disorders: Capillary leak syndrome has been reported and may be fatal (see Section 4.4 Special warnings and precautions for use).

- Infections and infestations: Bacterial, fungal and viral infections have been reported and may be fatal. These infections may lead to septic shock, respiratory failure and/or multi-organ failure (see Section 4.4 Special warnings and precautions for use).

    - *Systemic*: neutropenic sepsis, bacterial sepsis (Streptococcus, Enterococcus, Klebsiella), fungal sepsis (Candida), bacteraemia (Streptococcus).

    - *Respiratory*: bronchopulmonary aspergillosis, lung abscess, pneumonia bacterial (Klebsiella), lower respiratory tract infection, respiratory tract infection fungal.

    - *GI*: tonsillitis, hepatosplenic candidiasis.

    - *Neurological*: brain abscess, central nervous system infection.

    - *Musculoskeletal*: necrotizing fasciitis.

    - *Skin*: wound infection bacterial (Staphylococcus).

    - *Unspecified*: Cytomegalovirus, Fusarium, Pseudomonas, central line infection, vaginal cellulitis.

- Nervous system disorders: Syncope.

- Psychiatric disorders: Confusional state.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

No case of overdose has been reported. However, possible symptoms of overdose may include nausea, vomiting, diarrhoea and severe bone marrow depression. To date, the highest daily dose administered to human beings is 70 mg/m^2 for 5 consecutive days (2 paediatric

ALL patients). The toxicities observed in these patients included vomiting, hyperbilirubinaemia, elevated transaminase levels and maculo-papular rash.

Treatment

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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 inhibition of DNA synthesis / repair
- Ribonucleotide reductase inhibition with reduction of intracellular deoxynucleotide triphosphate (dNTP) pools
- Disruption of mitochondrial integrity with the release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing cells

In addition, halogenation of the adenine ring at the 2 position increases resistance to cellular degradation by adenosine deaminase, and substitution of a fluorine at the C-2' position in the arabino configuration decreases the susceptibility to phosphorylic cleavage by acid and bacterial purine nucleoside phosphorylase.

Pharmacodynamic effects:

In vitro studies have demonstrated that clofarabine inhibits cell growth and is cytotoxic to a variety of rapidly proliferating haematological and solid tumour cell lines (clofarabine concentrations inhibiting 50% of cell growth were ≤ 1 μM for solid tumours and mostly > 1 μM for leukaemia cell lines). It was also active against quiescent lymphocytes and macrophages (50% growth inhibition at > 0.45 μM). In addition, clofarabine delayed tumour growth and, in some cases, caused transient tumour regression in an assortment of human tumour xenografts implanted in mice.

Clinical trials

Seventy-eight (78) paediatric patients with Acute Lymphocytic Leukaemia (ALL) were exposed to Evoltra. Seventy (70) of the patients received the recommended paediatric dose of 52 mg/m^2 daily x 5 as an intravenous (IV) infusion.

Phase I Study in Paediatric Patients with Haematologic Malignancies

The safety and efficacy of Evoltra were evaluated in paediatric patients with refractory or relapsed haematologic malignancies in an open-label, dose-escalation, noncomparative study. The starting dose was 11.25 mg/m^2/day IV infusion daily x 5 and escalated to 70 mg/m^2/day IV infusion daily x 5. This dosing schedule was repeated every 2 to 6 weeks depending on toxicity and response. Nine of 17 ALL patients were treated with 52 mg/m^2 daily x 5. In the 17 ALL patients there were 2 complete remissions (12%) and 2 partial remissions (12%) at varying doses. Dose-limiting toxicities (DLTs) in this study were reversible hyperbilirubinaemia and elevated transaminase levels and skin rash, experienced at 70 mg/m^2. As a result of this study, the recommended dose for subsequent study in paediatric patients was determined to be 52 mg/m^2/day for 5 days.

Phase II Single Arm Study in Paediatric ALL

Evoltra was evaluated in an open-label, single arm study of 61 paediatric patients with relapsed/refractory ALL. Patients received a dose of 52 mg/m^2 over 2 hours for 5 consecutive days repeated every 2 to 6 weeks for up to 12 cycles. There was no dose escalation in this study.

All patients that had disease relapsed after and/or were refractory to two or more prior therapies. Most patients, 38/61 (62%) received > 2 prior regimens and 18/61 (30%) of the patients had undergone at least 1 prior transplant. The median age of the treated patients was 12 years (range 1-20 years old), 61% were male, 39% were female, 44% were Caucasian, 38% were Hispanic, 12% were African- American, 2% were Asian and 5% were of Other race.

The overall remission (OR) rate (Complete Remission [CR] + CR in the absence of total platelet recovery [CRp]), defined as no evidence of circulating blasts or extramedullary disease, an M1 bone marrow (≤ 5% blasts), and recovery of peripheral counts [platelets ≥ 100 x 10^9/L and absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L] and CRp, defined as meeting all criteria for CR except for recovery of platelet counts to > 100 x 10^9/L was evaluated. Partial Response (PR) was also determined, defined as complete disappearance of circulating blasts, an M2 bone marrow (≥ 5% and ≤ 25% blasts), and appearance of normal progenitor cells or an M1 marrow that did not qualify for CR or CRp. The remission criteria are based on those of the Children's Oncology Group. Duration of remission and overall survival was also evaluated. Transplantation rate was not a study endpoint.

Response rates for these studies were determined by an unblinded Independent Response Review Panel (IRRP).

Table 4 summarizes results for the paediatric ALL study. Responses were seen in both pre-B and T- cell immunophenotypes of ALL. The median cumulative dose was 530 mg (range 29-2815 mg) in 1 (41%), 2 (44%) or 3 or more (15%) cycles. The median number of cycles was 2 (range 1-12). The median time between cycles was 28 days with a range of 12 to 55 days.

Table 4: Response Rates in Paediatric ALL Study

N = 61			
Responses	**n**	**%**	**95% CI**
CR	7	11.5	4.7 to 22.2
CRp	5	8.2	2.7 to 18.1
PR	6	9.8	3.7 to 20.2
CR + CRp	12	19.7	10.6 to 31.8

Of 35 patients who were refractory to their immediately preceding induction regimen, 6 (17.1%) achieved a CR or CRp. Of 18 patients who had at least 1 prior haematopoietic stem cell transplant (HSCT), 5 (27.8%) achieved a CR or CRp.

Among the 18 patients who achieved at least a PR, 9 patients achieved the best response after 1 cycle of clofarabine, 8 patients required 2 courses and 1 patient achieved a CR after 3 cycles of therapy. Of these 18 responding patients, 9 had post-clofarabine bone marrow transplantation (3 CR, 3 CRp, 3 PR). Four of these patients who achieved CR or CRp received HSCT while in continued remission, one patient proceeded to transplant following relapse. One additional patient who achieved a CRp proceeded to transplant following alternative therapy. Duration of response was censored at the time of transplant.

The effect of clofarabine on remission duration and overall survival can only be accurately assessed for patients who did not undergo transplantation because of the confounding effect of transplantation. Of the six subjects with complete remission who did not undergo transplant, the median duration of remission was only 9 weeks (range 4 to 59). In the six who did receive transplant, the duration of remission ranged from 10 to 108+ weeks, some of the effect likely drug-related since longer remission may have enabled transplant.

Median overall survival was 63 weeks (range 9 to 72) for non-transplanted responding subjects. Overall survival ranged from 42 to 145+ weeks for transplanted responding subjects. The transplanted result reflects the effects of both clofarabine and the transplant.

Achievement of complete remission appears to have translated into opportunity for transplant and longer survival, but this needs confirmation.

Table 5 lists the individual remission duration and survival data for patients who achieved a CR or CRp.

Table 5: Duration of Remission and Survival for Patients who achieved CR or CRp in Paediatric ALL Study

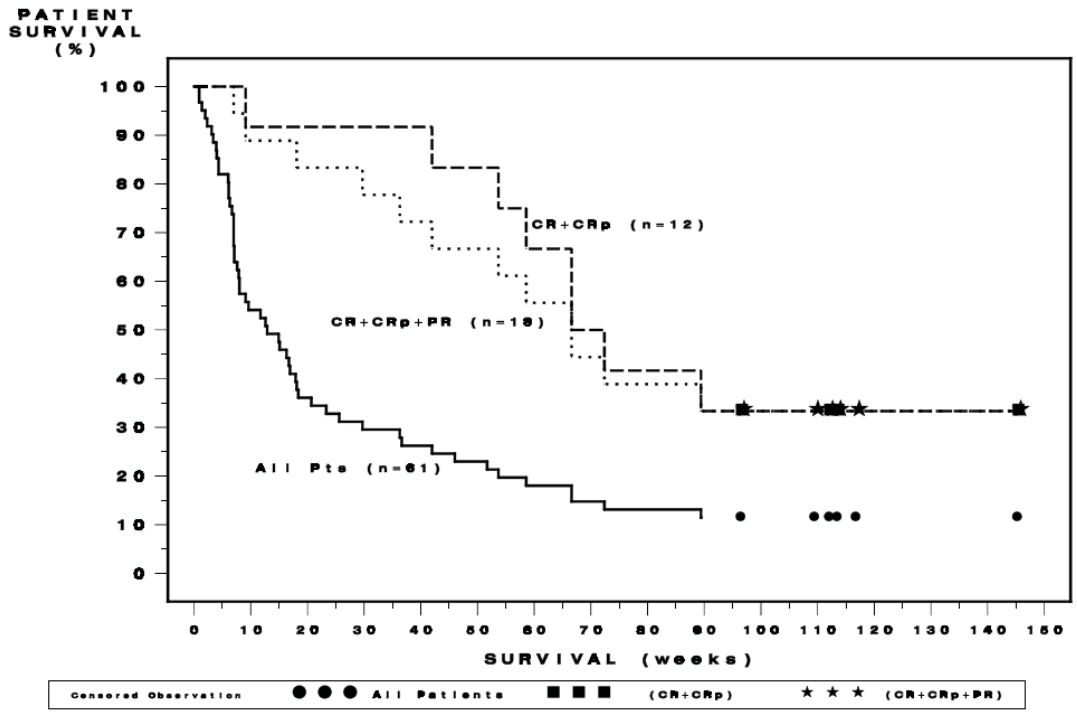
Best Response	Time to OR (weeks)	Duration of Remission (weeks)	Overall Survival (weeks)
Patients who did not undergo transplant			
CR	5.7	4.3	66.6
CR	14.3	6.1	58.6
CR	8.3	47.9	66.6
CRp	4.6	4.6	9.1
CR	3.3	58.6	72.4
CRp	3.7	11.7	53.7
Patients who underwent transplant while in continued remission*			
CRp	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

Figure 1:



Median overall survival for CR, CR + CRp, or CR + CRp + PR was 72.4, 69.5, 66.6 weeks respectively (Table 6). Median overall survival for all patients (n=61) was 12.9 weeks. Seven of 61 patients were alive at the time of last follow up (including 2 patients who achieved a PR).

Table 6: Overall Survival in Paediatric ALL Study

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored
Complete Remission	7	72.4	66.6	-	58.6	111.9	28.6
Complete Remission w/o Platelet Recovery	5	53.7	9.1	-	9.1	145.1	40.0
Partial Remission	6	33.0	18.1	-	7.0	116.6	33.3
Treatment Failure/Not Evaluable	43	7.6	6.7	12.6	0.9	150.3	2.3
Overall Remission (CR+CRp)	12	69.5	58.6	-	9.1	145.1	33.3
Complete or Partial Remission (CR+CRp+PR)	18	66.6	42.0	-	7.0	145.1	33.3
All Patients	61	12.9	7.9	18.1	0.9	150.3	11.5

5.2 PHARMACOKINETIC PROPERTIES

The population pharmacokinetics of Evoltra were studied in 40 paediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory acute lymphocytic leukaemia (ALL) or acute myelogenous leukaemia (AML). At the given 52 mg/m^2 dose, similar concentrations were obtained over a wide range of body surface areas (BSAs). Clofarabine was 47% bound to plasma proteins, predominantly to albumin (27% binding). Based on non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m^2 and 172 L/m^2, respectively. The terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics was observed between patients with ALL and AML or between males and females.

No relationship between clofarabine or clofarabine triphosphate exposure and toxicity or response was found in this population.

Based on 24-hour urine collections in the paediatric studies, 49 - 60% of the dose is excreted in the urine unchanged. *In vitro* studies using isolated human hepatocytes indicate very limited metabolism (0.2%). The pathways of non-hepatic elimination remain unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Clofarabine showed genotoxic activity in the *in vitro* mammalian cell chromosome aberration assay (CHO cells) and in the *in vivo* rat micronucleus assay. It did not show evidence of mutagenic activity in the bacterial mutation assay (Ames test).

Carcinogenicity

Clofarabine has not been tested for carcinogenic potential.

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 4.2 Dose and method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

For shelf life of the diluted medicinal product, see Section 4.2 Dose and method of administration, Stability.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

For storage conditions of the diluted medicinal product, see Section 4.2 Dose and method of administration, Stability.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in single packs of 20 mL clear type I glass vials.

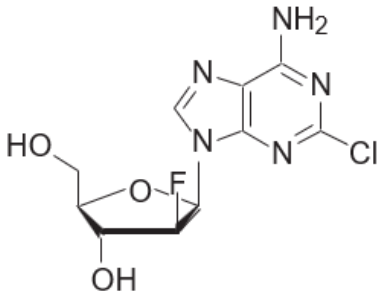
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Clofarabine is a purine nucleoside anti-metabolite structurally related to marketed substances like fludarabine and cladribine. It is a white to off-white solid which is soluble in saline up to 1.5 mg/mL at room temperature. The optical rotation is + 39.93° (average; c = 5 mg/mL, 25°C) in dimethylformamide solvent. The alcohol pKa is 16, the amine pKa is 12, and the protonated base pKa is approximately 2.

Chemical structure



Chemical Name

2-chloro-9-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-9H-purine-6-amine.

Molecular Formula

$C_{10}H_{11}ClFN_5O_3$

Molecular Weight

303.68

CAS number

123318-82-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

25 September 2009

10 DATE OF REVISION

21 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address updated