

CLOFARABINE - clofarabine injection

Apotex Corp.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLOFARABINE INJECTION safely and effectively. See full prescribing information for CLOFARABINE INJECTION.

CLOFARABINE injection, for intravenous use

Initial U.S. Approval: 2004

----- **INDICATIONS AND USAGE** -----

Clofarabine injection is a nucleoside metabolic inhibitor indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with clofarabine injection. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Administer the recommended pediatric dose of 52 mg/m² as an intravenous infusion over 2 hours daily for 5 consecutive days of a 28-day cycle. Repeat cycles every 2-6 weeks. (2.1)
- Provide supportive care, such as intravenous infusion fluids, antihyperuricemic treatment, and alkalization of urine throughout the 5 days of clofarabine injection administration to reduce the risk of tumor lysis and other adverse reactions. (2.1)
- Discontinue clofarabine injection if hypotension develops during the 5 days of administration. (2.1)
- Reduce the dose in patients with renal impairment. (2.2)
- Use dose modification for toxicity. (2.4)

----- **DOSAGE FORMS AND STRENGTHS** -----

- Injection: 20 mg/20 mL (1 mg/mL) single-dose vial. (3)

----- **CONTRAINDICATIONS** -----

- None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Myelosuppression: May be severe and prolonged. Monitor complete blood counts and platelet counts during clofarabine injection therapy. (5.1)
- Hemorrhage: Serious and fatal cerebral, gastrointestinal and pulmonary hemorrhage. Monitor platelets and coagulation parameters and treat accordingly. (5.2)
- Infections: Severe and fatal sepsis as a result of bone marrow suppression. Monitor for signs and symptoms of infection; discontinue clofarabine injection and treat promptly. (5.3)
- Tumor Lysis syndrome: Anticipate, monitor for signs and symptoms and treat promptly. (5.4)
- Systemic Inflammatory Response Syndrome (SIRS) or Capillary Leak Syndrome: Monitor for and discontinue clofarabine injection immediately if suspected. (5.5)
- Venous Occlusive Disease of the Liver: Monitor for and discontinue clofarabine injection if suspected. (5.6)
- Hepatotoxicity: Severe and fatal hepatotoxicity. Monitor liver function, for signs and symptoms of hepatitis and hepatic failure. Discontinue clofarabine injection immediately for Grade 3 or greater liver enzyme and/or bilirubin elevations. (5.7)
- Renal Toxicity: Increased creatinine and acute renal failure; monitor renal function and interrupt or discontinue clofarabine injection. (5.8)
- Enterocolitis: Serious and fatal enterocolitis, occurring more frequently within 30 days of treatment and with combination chemotherapy. Monitor patients for signs and symptoms of enterocolitis and treat promptly. (5.9)
- Skin Reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases. Discontinue for exfoliative or bullous rash, or if SJS or TEN is suspected. (5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. (5.11)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (≥25%): vomiting, nausea, diarrhea, febrile neutropenia, pruritus, headache, bacteremia, pyrexia, rash, tachycardia, abdominal pain, chills, fatigue, anorexia, pain in extremity, hypotension, epistaxis, and petechiae. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Clofarabine injection is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with clofarabine injection.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer the recommended pediatric dose of 52 mg/m² as an intravenous infusion over 2 hours daily for 5 consecutive days.

- Repeat treatment cycles following recovery or return to baseline organ function, approximately every 2 to 6 weeks. Base dosage on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle. To prevent drug incompatibilities, do not administer other medications through the same intravenous line. Administer subsequent cycles no sooner than 14 days from the starting day of the previous cycle and provided the patient's ANC is $\geq 0.75 \times 10^9/L$.
- Provide supportive care, such as intravenous fluids, antihyperuricemic treatment, and alkalinize urine throughout the 5 days of clofarabine injection administration to reduce the effects of tumor lysis and other adverse reactions.
- Discontinue clofarabine injection if hypotension develops during the 5 days of administration.
- Monitor renal and hepatic function during the 5 days of clofarabine injection administration [see *Warnings and Precautions (5.7, 5.8)*].
- Monitor patients taking medications known to affect blood pressure. Monitor cardiac function during administration of clofarabine injection.

2.2 Recommended Dosage Reduction for Renal Impairment

- Reduce the dose by 50% in patients with creatinine clearance (CrCL) between 30 and 60 mL/min. There is insufficient information to make a dosage recommendation in patients with CrCL less than 30 mL/min [see *Use in Specific Populations (8.7)*].

2.3 Potential Concomitant Medications and Medications to Avoid

- Consider prophylactic antiemetic medications as clofarabine injection is moderately emetogenic.
- Consider the use of prophylactic steroids to mitigate Systemic Inflammatory Response Syndrome (SIRS) or capillary leak syndrome (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema).
- Minimize exposure to drugs with known renal toxicity during the 5 days of clofarabine injection administration since the risk of renal toxicity may be increased.
- Avoid concomitant use of medications known to induce hepatic toxicity.

2.4 Dose Modifications and Reinitiation of Therapy after Adverse Reactions

Hematologic Toxicity

- If a patient experiences a Grade 4 neutropenia (ANC $< 0.5 \times 10^9/L$) lasting ≥ 4 weeks, reduce

dose by 25% for the next cycle.

Non-hematologic Toxicity

- Withhold clofarabine injection if a patient develops a clinically significant infection, until the infection is controlled, then restart at the full dose.
- Withhold clofarabine injection for a Grade 3 non-infectious non-hematologic toxicity (excluding transient elevations in serum transaminases and/or serum bilirubin and/or nausea/vomiting controlled by antiemetic therapy). Re-institute clofarabine injection administration at a 25% dose reduction when resolution or return to baseline.
- Discontinue clofarabine injection administration for a Grade 4 non-infectious non-hematologic toxicity.
- Discontinue clofarabine injection administration if a patient shows early signs or symptoms of SIRS or capillary leak syndrome (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema) occur and provide appropriate supportive measures.
- Discontinue clofarabine injection administration if Grade 3 or higher increases in creatinine or bilirubin are noted. Re-institute clofarabine injection with a 25% dose reduction, when the patient is stable and organ function has returned to baseline. If hyperuricemia is anticipated (tumor lysis), initiate measures to control uric acid.

2.5 Reconstitution/Preparation

Filter Clofarabine injection through a sterile 0.2 micron syringe filter and then dilute with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion to a final concentration between 0.15 mg/mL and 0.4 mg/mL. Use within 24 hours of preparation. Store diluted clofarabine injection at room temperature (15°C to 30°C).

Discard unused portion in vial.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 mg/20 mL (1 mg/mL) clear colorless solution in single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Clofarabine injection causes myelosuppression which may be severe and prolonged. Febrile neutropenia occurred in 55% and non-febrile neutropenia in an additional 10% of pediatric patients in clinical trials. At initiation of treatment, most patients in the clinical studies had hematological impairment as a manifestation of leukemia. Myelosuppression is usually reversible with interruption of clofarabine injection treatment and appears to be dose-dependent. Monitor complete blood counts [*see Dosage and Administration (2.4)*].

5.2 Hemorrhage

Serious and fatal hemorrhage, including cerebral, gastrointestinal and pulmonary hemorrhage, has occurred. The majority of the cases were associated with thrombocytopenia. Monitor platelets and coagulation parameters and treat accordingly [*see Adverse Reactions (6.2)*].

5.3 Infections

Clofarabine injection increases the risk of infection, including severe and fatal sepsis, and opportunistic infections. At baseline, 48% of the pediatric patients had one or more concurrent infections. A total of 83% of patients experienced at least one infection after clofarabine injection treatment, including fungal, viral and bacterial infections. Monitor patients for signs and symptoms of infection, discontinue clofarabine injection, and treat promptly.

5.4 Tumor Lysis Syndrome

Administration of clofarabine injection may result in tumor lysis syndrome associated with the breakdown metabolic products from peripheral leukemia cell death. Monitor patients undergoing treatment for signs and symptoms of tumor lysis syndrome and initiate preventive measures including adequate intravenous fluids and measures to control uric acid.

5.5 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome

Clofarabine injection may cause a cytokine release syndrome (e.g., tachypnea, tachycardia, hypotension, pulmonary edema) that may progress to the systemic inflammatory response syndrome (SIRS) with capillary leak syndrome and organ impairment which may be fatal. Monitor patients frequently for these conditions. In clinical trials, SIRS was reported in two patients (2%); capillary leak syndrome was reported in four patients (4%). Symptoms included rapid onset of respiratory distress, hypotension, pleural and pericardial effusion, and multiorgan failure. Close monitoring for this syndrome and early intervention may reduce the risk. Immediately discontinue clofarabine injection and provide appropriate supportive measures. The use of prophylactic steroids (e.g., 100 mg/m² hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak syndrome. Consider use of diuretics and/or albumin. After the patient is stabilized and organ function has returned to baseline, retreatment with clofarabine injection can be considered with a 25% dose reduction.

5.6 Venous Occlusive Disease of the Liver

Patients who have previously received a hematopoietic stem cell transplant (HSCT) are at higher risk for veno-occlusive disease (VOD) of the liver following treatment with clofarabine (40 mg/m²) when used in combination with etoposide (100 mg/m²) and cyclophosphamide (440 mg/m²). Severe hepatotoxic events have been reported in a combination study of clofarabine in pediatric patients with relapsed or refractory acute leukemia. Two cases (2%) of VOD in the monotherapy studies were considered related to study drug. Monitor for and discontinue clofarabine injection if VOD is suspected.

5.7 Hepatotoxicity

Severe and fatal hepatotoxicity, including hepatitis and hepatic failure, has occurred with the use of clofarabine injection. In clinical studies, Grade 3-4 liver enzyme elevations were observed in pediatric patients during treatment with clofarabine injection at the following rates: elevated aspartate aminotransferase (AST) occurred in 36% of patients; elevated alanine aminotransferase (ALT) occurred in 44% of patients. AST and ALT elevations typically occurred within 10 days of clofarabine injection administration and returned to Grade 2 or less within 15 days. Grade 3 or 4 elevated bilirubin occurred in 13% of patients, with 2 events reported as Grade 4 hyperbilirubinemia (2%), one of which resulted in treatment discontinuation and one patient had multiorgan failure and died. Eight patients (7%) had Grade 3 or 4 elevations in serum bilirubin at the last time point measured; these patients died due to sepsis and/or multiorgan failure. Monitor hepatic function, and for signs and symptoms of hepatitis and hepatic failure. Discontinue clofarabine injection immediately for Grade 3 or greater liver enzyme and/or bilirubin elevations [see *Dosage and Administration* (2.4)].

5.8 Renal Toxicity

Clofarabine injection may cause acute renal failure. In clofarabine injection treated patients in clinical studies, Grade 3 or 4 elevated creatinine occurred in 8% of patients and acute renal failure was

reported as Grade 3 in three patients (3%) and Grade 4 in two patients (2%). Patients with infection, sepsis, or tumor lysis syndrome may be at increased risk of renal toxicity when treated with clofarabine injection. Hematuria occurred in 13% of clofarabine injection treated patients overall. Monitor patients for renal toxicity and interrupt or discontinue clofarabine injection as necessary [see *Dosage and Administration* (2.4)].

5.9 Enterocolitis

Fatal and serious cases of enterocolitis, including neutropenic colitis, cecitis, and *C. difficile* colitis, have occurred 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, hemorrhage or sepsis complications. Monitor patients for signs and symptoms of enterocolitis and treat promptly.

5.10 Skin Reactions

Serious and fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Discontinue clofarabine for exfoliative or bullous rash, or if SJS or TEN is suspected [see *Adverse Reactions* (6.2)].

5.11 Embryo-Fetal Toxicity

Based on findings from animal reproductive studies and the drug's mechanism of action, clofarabine can cause fetal harm when administered to a pregnant woman. Intravenous doses of clofarabine in rats and rabbits administered during organogenesis at doses that were below the maximum recommended human dose of 52 mg/m² based on body surface area (mg/m²) caused an increase in resorptions, malformations, and variations. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment with clofarabine and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with clofarabine and for at least 3 months after the last dose [see *Use in Specific Populations* (8.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the label:

- Myelosuppression [see *Warnings and Precautions* (5.1)]
- Hemorrhage [see *Warnings and Precautions* (5.2)]
- Serious Infections [see *Warnings and Precautions* (5.3)]
- Hyperuricemia (tumor lysis syndrome) [see *Warnings and Precautions* (5.4)]
- Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome [see *Warnings and Precautions* (5.5)]
- Venous Occlusive Disease of the Liver [see *Warnings and Precautions* (5.6)]
- Hepatotoxicity [see *Warnings and Precautions* (5.7)]
- Renal Toxicity [see *Warnings and Precautions* (5.8)]
- Enterocolitis [see *Warnings and Precautions* (5.9)]
- Skin Reactions [see *Warnings and Precautions* (5.10)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to clofarabine injection in 115 pediatric patients with relapsed or refractory Acute Lymphoblastic Leukemia (ALL) (70 patients) or Acute Myelogenous

Leukemia (AML) (45 patients).

In total, 115 pediatric patients treated in clinical trials received the recommended dose of clofarabine injection 52 mg/m² daily × 5. The median number of cycles was 2. The median cumulative amount of clofarabine injection received by pediatric patients during all cycles was 540 mg.

Most common adverse reactions (≥25%): vomiting, nausea, diarrhea, febrile neutropenia, pruritus, headache, bacteremia, pyrexia, rash, tachycardia, abdominal pain, chills, fatigue, anorexia, pain in extremity, hypotension, epistaxis, and petechiae.

Table 1 lists adverse reactions by System Organ Class, including severe or life-threatening (NCI CTCAE Grade 3 or Grade 4), reported in ≥ 5% of the 115 patients in the 52 mg/m²/day dose group (pooled analysis of pediatric patients with ALL and AML). More detailed information and follow-up of certain events is given below.

Table 1: Most Commonly Reported (≥ 5% Overall) Adverse Reactions by System Organ Class (N=115 pooled analysis)

System Organ Class ¹	Adverse Reaction (MedDRA Preferred Term) ¹	ALL/AML (All Grades, N=115)		Worst Grade (NCI Common Terminology Criteria) ¹					
				3		4		5	
		N	%	N	%	N	%	N	%
Blood and Lymphatic System Disorders	Febrile neutropenia	63	55	59	51	3	3	.	.
	Neutropenia	11	10	3	3	8	7	.	.
Cardiac Disorders	Pericardial effusion	9	8	.	.	1	1	.	.
	Tachycardia	40	35	6	5
Gastrointestinal Disorders	Abdominal pain	40	35	8	7
	Abdominal pain upper	9	8	1	1
	Diarrhea	64	56	14	12
	Gingival or mouth bleeding	20	17	8	7	1	1	.	.
	Nausea	84	73	16	14	1	1	.	.
	Oral mucosal petechiae	6	5	4	4
	Proctalgia	9	8	2	2
	Stomatitis	8	7	1	1
	Vomiting	90	78	9	8	1	1	.	.
	General Disorders and Administration Site Conditions	Asthenia	12	10	1	1	1	1	.
Chills		39	34	3	3
Fatigue		39	34	3	3	2	2	.	.
Irritability		11	10	1	1
Mucosal inflammation		18	16	2	2
Edema		14	12	2	2
Pain		17	15	7	6	1	1	.	.
Pyrexia		45	39	16	14
Hepatobiliary Disorder	Jaundice	9	8	2	2
Infections and Infestations	Bacteremia	10	9	10	9
	Candidiasis	8	7	1	1
	Catheter related infection	14	12	13	11
	Cellulitis	9	8	7	6
	Clostridium colitis	8	7	6	5

	Herpes simplex	11	10	6	5
	Herpes zoster	8	7	6	5
	Oral candidiasis	13	11	2	2
	Pneumonia	11	10	6	5	1	1	1	1

¹ Patients with more than one adverse reaction (MedDRA preferred term) within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same adverse reaction (MedDRA preferred term) are counted only once within that reaction and at the highest severity grade.

Table 1: Most Commonly Reported ($\geq 5\%$ Overall) Adverse Reactions by System Organ Class (N=115 pooled analysis) (Continued)

System Organ Class ¹	Adverse Reaction (MedDRA Preferred Term) ¹	ALL/AML (All Grades, N=115)		Worst Grade (NCI Common Terminology Criteria) ¹					
				3		4		5	
		N	%	N	%	N	%	N	%
Infections and Infestations (continued)	Sepsis, including septic shock	19	17	6	5	4	4	9	8
	Staphylococcal bacteremia	7	6	5	4	1	1	.	.
	Staphylococcal sepsis	6	5	5	4	1	1	.	.
	Upper respiratory tract infection	6	5	1	1
Metabolism and Nutrition Disorders	Anorexia	34	30	6	5	8	7	.	.
Musculoskeletal and Connective Tissue Disorders	Arthralgia	10	9	3	3
	Back pain	12	10	3	3
	Bone pain	11	10	3	3
	Myalgia	16	14
	Pain in extremity	34	30	6	5
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	Tumor lysis syndrome	7	6	7	6
Nervous System Disorders	Headache	49	43	6	5
	Lethargy	12	10	1	1
	Somnolence	11	10	1	1
Psychiatric Disorders	Agitation	6	5	1	1
	Anxiety	24	21	2	2
Renal and Urinary Disorders	Hematuria	15	13	2	2
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	15	13	6	5	2	2	.	.
	Epistaxis	31	27	15	13
	Pleural effusion	14	12	4	4	2	2	.	.
	Respiratory distress	12	10	5	4	4	4	1	1
	Tachypnea	10	9	4	4	1	1	.	.
Skin and Subcutaneous Tissue Disorders	Erythema	13	11
	Palmar-plantar erythrodysesthesia syndrome	18	16	8	7
	Petechiae	30	26	7	6

	Pruritus	49	43	1	1
	Rash	44	38	8	7
	Rash pruritic	9	8
Vascular Disorders	Flushing	22	19
	Hypertension	15	13	6	5
	Hypotension	33	29	13	11	9	8	.	.

¹ Patients with more than one adverse reaction (MedDRA preferred term) within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same adverse reaction (MedDRA preferred term) are counted only once within that reaction and at the highest severity grade.

The following adverse reactions were reported in <5% of the 115 pediatric patients with ALL or AML:

Gastrointestinal Disorders: cecitis, pancreatitis

Hepatobiliary Disorders: hyperbilirubinemia

Immune System Disorders: hypersensitivity

Infections and Infestations: bacterial infection, Enterococcal bacteremia, Escherichia bacteremia, Escherichia sepsis, fungal infection, fungal sepsis, gastroenteritis adenovirus, infection, influenza, parainfluenza virus infection, pneumonia fungal, pneumonia primary atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection

Investigations: blood creatinine increased

Psychiatric Disorders: mental status change

Respiratory, Thoracic and Mediastinal Disorder: pulmonary edema

Table 2 lists the incidence of treatment-emergent laboratory abnormalities after clofarabine injection administration at 52 mg/m² among pediatric patients with ALL and AML (N=115).

Table 2: Incidence of Treatment-Emergent Laboratory Abnormalities after Clofarabine Injection Administration

Parameter	Any Grade	Grade 3 or higher
Anemia (N=114)	83%	75%
Leukopenia (N=114)	88%	88%
Lymphopenia (N=113)	82%	82%
Neutropenia (N=113)	64%	64%
Thrombocytopenia (N=114)	81%	80%
Elevated Creatinine (N=115)	50%	8%
Elevated SGOT (N=100)	74%	36%
Elevated SGPT (N=113)	81%	43%
Elevated Total Bilirubin (N=114)	45%	13%

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of clofarabine injection. 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.

- Gastrointestinal disorders: gastrointestinal hemorrhage including fatalities.
- Metabolism and nutrition disorders: hyponatremia
- Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal

necrolysis (TEN) (including fatal cases).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal reproduction studies, intravenous administration of clofarabine to pregnant rats and rabbits during organogenesis at doses approximately 0.2 to 1-times the maximum recommended human dose of 52 mg/m² based on body surface area (BSA) resulted in embryo-fetal mortality, alterations to growth, and structural abnormalities (see Data). Advise pregnant women of the potential risk to a fetus. There are no available data on clofarabine use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Clofarabine should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

Intravenous administration of clofarabine to pregnant rats during organogenesis (gestation days [GD] 7 to 17) at doses of 1, 3 or 9 mg/kg/day (equivalent to 6, 18, 54 mg/m²/day) resulted in maternal toxicities at the 9 mg/kg dose, as indicated by reduced body weights and food consumption. Developmental toxicity (i.e., reduced fetal body weights and increased postimplantation loss) and increased incidences of external, soft tissue, and skeletal malformations and variations (including retarded ossification) were observed at 9 mg/kg/day (54 mg/m²; approximately equivalent to the recommended human dose based on BSA). Altered ossification patterns (extra metacarpal or metatarsal ossification) were observed in single fetuses at lower doses of clofarabine (1 and 3 mg/kg/day; 0.1- and 0.3-times the recommended human dose based on BSA).

When clofarabine was administered intravenously to pregnant rabbits during organogenesis (GD 6 to 18) at doses of 0.1, 0.3, or 1 mg/kg/day (equivalent to 1.2, 3.6, 12 mg/m²/day), developmental toxicity (i.e., reduced fetal body weights and increased postimplantation loss) and increased incidences of external, soft tissue, and skeletal malformations and variations (including retarded ossification) were observed at the 1 mg/kg/day dose (12 mg/m²; 0.2-times the recommended human dose based on BSA). Alterations in ossification patterns (increase in the average numbers of ossified thoracic vertebrae and rib pairs, and reduction in the average number of forepaw metacarpals) and abdominal wall defect were observed at 0.3 mg/kg/day (3.6 mg/m²; 0.1-times the recommended human dose based on BSA).

8.2 Lactation

Risk Summary

There are no data on the presence of clofarabine in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child including genotoxicity, advise patients not to breastfeed during treatment with clofarabine, and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating clofarabine.

Contraception

Females

Clofarabine can cause embryo-fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise female patients to use effective contraception during treatment with clofarabine and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with clofarabine and for at least 3 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Females

Based on findings from animal studies, clofarabine may impair female fertility [*see Nonclinical Toxicology (13.1)*]. The reversibility of the effect on fertility is unknown.

Males

Based on findings from animal studies, clofarabine may impair male fertility [*see Nonclinical Toxicology (13.1)*]. The reversibility of the effect on fertility is unknown.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia.

8.5 Geriatric Use

Safety and effectiveness of clofarabine injection has not been established in geriatric patients aged 65 and older.

8.6 Adults with Hematologic Malignancies

Safety and effectiveness have not been established in adults.

8.7 Renal Impairment

Reduce the clofarabine starting dose by 50% in patients with CrCL of 30 to 60 mL/min. There is insufficient information to make a dosage recommendation in patients with CrCL less than 30 mL/min or in patients on dialysis.

The pharmacokinetics of clofarabine in patients with renal impairment and normal renal function were obtained from a population pharmacokinetic analysis of three pediatric and two adult studies. In patients with CrCL 60 to less than 90 mL/min (N = 47) and CrCL 30 to less than 60 mL/min (N = 30), the average AUC of clofarabine increased by 60% and 140%, respectively, compared to patients with normal (N = 66) renal function (CrCL greater than 90 mL/min).

10 OVERDOSAGE

There were no known overdoses of clofarabine injection. The highest daily dose administered to a human to date (on a mg/m² basis) has been 70 mg/m²/day × 5 days (2 pediatric ALL patients). The toxicities included in these 2 patients included Grade 4 hyperbilirubinemia, Grade 2 and 3 vomiting, and Grade 3 maculopapular rash.

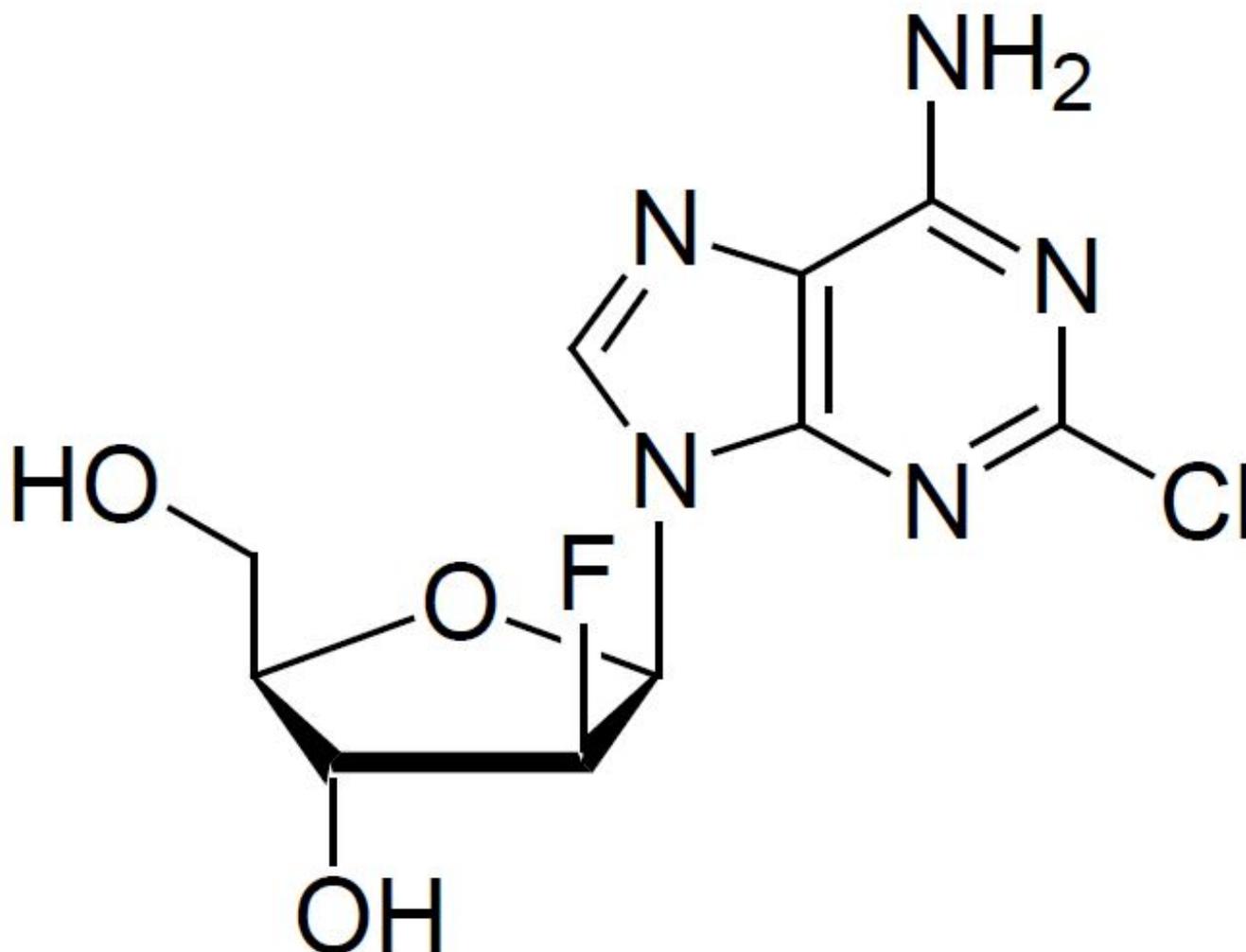
In a Phase 1 study of adults with refractory and/or relapsed hematologic malignancies, the recommended pediatric dose of 52 mg/m²/day was not tolerated.

11 DESCRIPTION

Clofarabine injection contains clofarabine, a purine nucleoside metabolic inhibitor.

The chemical name of clofarabine is 2-chloro-9-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-9H-purine-6-amine. Its molecular formula is C₁₀H₁₁ClFN₅O₃ with a molecular weight of 303.68 Daltons.

The molecular structure of clofarabine is:



Clofarabine injection (1 mg/mL) is supplied in a 20 mL, single-dose vial. The 20 mL vial contains 20 mg clofarabine formulated in 20 mL unbuffered normal saline (comprised of Water for Injection, USP, and Sodium Chloride, USP). The pH range of the solution is 4.5 to 7.5. The solution is sterile, clear and practically colorless, and is preservative-free.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clofarabine is sequentially metabolized intracellularly to the 5'-monophosphate metabolite by deoxycytidine kinase and mono- and di-phospho-kinases to the active 5'-triphosphate metabolite. Clofarabine has affinity for the activating phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide

reductase, and by terminating DNA chain elongation and inhibiting repair through incorporation into the DNA chain by competitive inhibition of DNA polymerases. The affinity of clofarabine triphosphate for these enzymes is similar to or greater than that of deoxyadenosine triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor, leading to programmed cell death.

Clofarabine is cytotoxic to rapidly proliferating and quiescent cancer cell types *in vitro*.

12.3 Pharmacokinetics

The population pharmacokinetics of clofarabine injection were studied in 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). At the given 52 mg/m² dose, similar concentrations were obtained over a wide range of body surface areas (BSAs). Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on non-compartmental analysis, systemic clearance and volume of distribution at steady-state were 28.8 L/h/m² and 172 L/m², respectively. The terminal half-life was 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 pediatric studies, 49% to 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.

Clofarabine has not been studied in patients with hepatic impairment.

Drug-Drug Interactions

In vitro studies suggested that clofarabine undergoes limited metabolism and does not inhibit or induce major CYP enzymes. CYP inhibitors and inducers are unlikely to affect the metabolism of clofarabine. Clofarabine is unlikely to affect the metabolism of CYP substrates. However, no *in vivo* drug interaction studies have been conducted.

An *in vitro* transporter study suggested that clofarabine is a substrate of human transporters OAT1, OAT3, and OCT1. A preclinical study using perfused rat kidney demonstrated that the renal excretion of clofarabine was decreased by cimetidine, an inhibitor of the hOCT2. Although the clinical implications of this finding have not been determined, signs of clofarabine injection toxicity should be monitored when administered with other hOAT1, hOAT3, hOCT1 and hOCT2 substrates or inhibitors.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Clofarabine has not been tested for carcinogenic potential.

Clofarabine was clastogenic in the *in vitro* mammalian cell chromosome aberration assay (CHO cells) and in the *in vivo* rat micronucleus assay. Clofarabine was not mutagenic in the bacterial mutation assay (Ames test).

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 doses of 3 mg/kg/day (approximately 0.2-times the recommended human dose based on body surface area [BSA]). Rats receiving 25 mg/kg/day (approximately 3-times the recommended human dose based on BSA) in a 6-month intravenous study had testicular findings of bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial

cells. In a 6-month intravenous dog study, cell degeneration of the epididymis and degeneration of the seminiferous epithelium in the testes were observed at 0.375 mg/kg/day (approximately 0.1-times the recommended human dose on a BSA basis). Ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at 75 mg/kg/day (approximately 4-times the recommended human dose on a mg/m² basis), the only dose administered to female mice.

14 CLINICAL STUDIES

Seventy-eight (78) pediatric patients with ALL were exposed to clofarabine injection. Seventy (70) of the patients received the recommended pediatric dose of clofarabine injection 52 mg/m² daily for 5 days as an intravenous infusion.

Dose Escalation Study in Pediatric Patients with Hematologic Malignancies

The safety and efficacy of clofarabine injection were evaluated in pediatric patients with refractory or relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study (NCT00042341, A Phase II, Open Label Study of Clofarabine in Pediatric Patients With Refractory or Relapsed Acute Lymphoblastic Leukemia). The starting dose of clofarabine injection was 11.25 mg/m²/day intravenous infusion daily X 5 and escalated to 70 mg/m²/day intravenous 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 clofarabine injection 52 mg/m² daily for 5 days. In the 17 ALL patients there were 2 complete remissions (12%) and 2 partial remissions (12%) at varying doses. Dose-limiting toxicities in this study were reversible hyperbilirubinemia and elevated transaminase levels and skin rash, experienced at 70 mg/m². As a result of this study, the recommended dose for subsequent study in pediatric patients was determined to be 52 mg/m²/day for 5 days.

Single-Arm Study in Pediatric ALL

Clofarabine injection was evaluated in an open-label, single-arm study of 61 pediatric patients with relapsed/refractory ALL. Patients received a dose of 52 mg/m² intravenous infusion 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 had disease that had relapsed after and/or was refractory to two or more prior therapies. Most patients, 38/61 (62%), had 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, 61% were male, 39% were female, 44% were Caucasian, 38% were Hispanic, 12% were African-American, 2% were Asian and 5% were Other race.

The overall remission (OR) rate (Complete Remission [CR] + CR in the absence of total platelet recovery [CRp]) was evaluated. CR was defined as no evidence of circulating blasts or extramedullary disease, an M1 bone marrow ($\leq 5\%$ blasts), and recovery of peripheral counts [platelets $\geq 100 \times 10^9/L$ and absolute neutrophil count (ANC) $\geq 1 \times 10^9/L$]. CRp was defined as meeting all criteria for CR except for recovery of platelet counts to $\geq 100 \times 10^9/L$. Partial Response (PR) was also determined, defined as complete disappearance of circulating blasts, an M2 bone marrow ($\geq 5\%$ and $\leq 25\%$ blasts), and appearance of normal progenitor cells or an M1 marrow that did not qualify for CR or CRp. Duration of remission 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 3 summarizes results for the pediatric 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 3: Results in Single-Arm Pediatric ALL

	N = 61
CR % [95% CI]	11.5 (4.7, 22.2)
CRp % [95% CI]	8.2 (2.7, 18.1)
Median Duration of CR plus CRp (range in weeks) ¹	10.7 (4.3 to 58.6)

CR = Complete response

CRp = Complete response without platelet recovery

¹ Does not include 4 patients who were transplanted (duration of response, including response after transplant, in these 4 patients was 28.6 to 107.7 weeks).

Six (9.8%) patients achieved a PR; the clinical relevance of a PR in this setting is unknown.

Of 35 patients who were refractory to their immediately preceding induction regimen, 6 (17%) achieved a CR or CRp. Of 18 patients who had at least 1 prior hematopoietic stem cell transplant (HSCT), 5 (28%) achieved a CR or CRp.

Among the 12 patients who achieved at least a CRp, 6 patients achieved the best response after 1 cycle of clofarabine, 5 patients required 2 courses and 1 patient achieved a CR after 3 cycles of therapy.

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*.
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

16 HOW SUPPLIED/STORAGE AND HANDLING

Clofarabine injection is supplied in single-dose 20 mL clear tubular USP Type-I vials containing 20 mg of clofarabine in 20 mL of solution. Each box contains one clofarabine injection vial (NDC 60505-6166-0). The 20-mL tubular USP Type-I clear vials contain 20 mL (20 mg) of solution. The pH range of the solution is 4.5 to 7.5.

The solution is clear colorless, is free from visible particle matter.

Vials containing undiluted clofarabine injection should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Clofarabine injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Hematologic Toxicity

Advise patients to return for regular blood counts and to report any symptoms associated with hematologic toxicity (such as weakness, fatigue, pallor, shortness of breath, easy bruising, petechiae, purpura, fever) to their physician [*see Warnings and Precautions (5.1)*].

Infection

Advise patients of the signs or symptoms of infection (e.g., fever) and report to the physician immediately if any occur [*see Warnings and Precautions (5.3)*].

Hepatic and Renal Toxicity

Advise patients to avoid medications including over the counter and herbal medications, which may be hepatotoxic or nephrotoxic, during the 5 days of clofarabine injection administration. Also, advise

patients of the possibility of developing liver function abnormalities and to immediately report signs or symptoms of jaundice. Advise patients of the signs or symptoms of renal failure/acute renal failure [see *Warnings and Precautions (5.7) (5.8)*].

Systemic Inflammatory Response Syndrome (SIRS)/Capillary Leak Syndrome

Advise patients of the signs or symptoms of SIRS, such as fever, tachycardia, tachypnea, dyspnea and symptoms suggestive of hypotension [see *Warnings and Precautions (5.5)*].

Pregnancy

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.11), Use in Specific Populations (8.3)*]. Advise female patients of reproductive potential to use effective contraception during treatment with clofarabine injection and for at least 6 months after the last dose [see *Use in Specific Populations (8.3)*]. Advise males with female partners of reproductive potential to use effective contraception during treatment with clofarabine injection and for at least 3 months after the last dose [see *Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Lactation

Advise females not to breastfeed during treatment with clofarabine injection and for 2 weeks after the last dose [see *Use in Specific Populations (8.2)*].

Gastrointestinal Disorders

Advise patients that they may experience nausea, vomiting, and/or diarrhea with clofarabine injection. If these symptoms are significant, they should seek medical attention [see *Warnings and Precautions (5.9)*].

Rash

Advise patients that they may experience skin rash with clofarabine injection. If this symptom is significant, they should seek medical attention.

Manufactured by: MSN Laboratories Private Limited,
Nandigama,
Telangana 509216, India
M.L.No.: 5/MN/TS/2014/F/G

Manufactured for: Apotex Corp.,
Weston, Florida, 33326

Revised: 1/2020

Package Label - Principal Display Panel – 1 (20 mL) Single-Dose Vial (Carton label)

NDC 60505-6166-0

Clofarabine Injection

20 mg/20 mL (1 mg/mL)

Must Be Diluted Prior To Intravenous Use

Contains 1 (20 mL) Single-Dose Vial

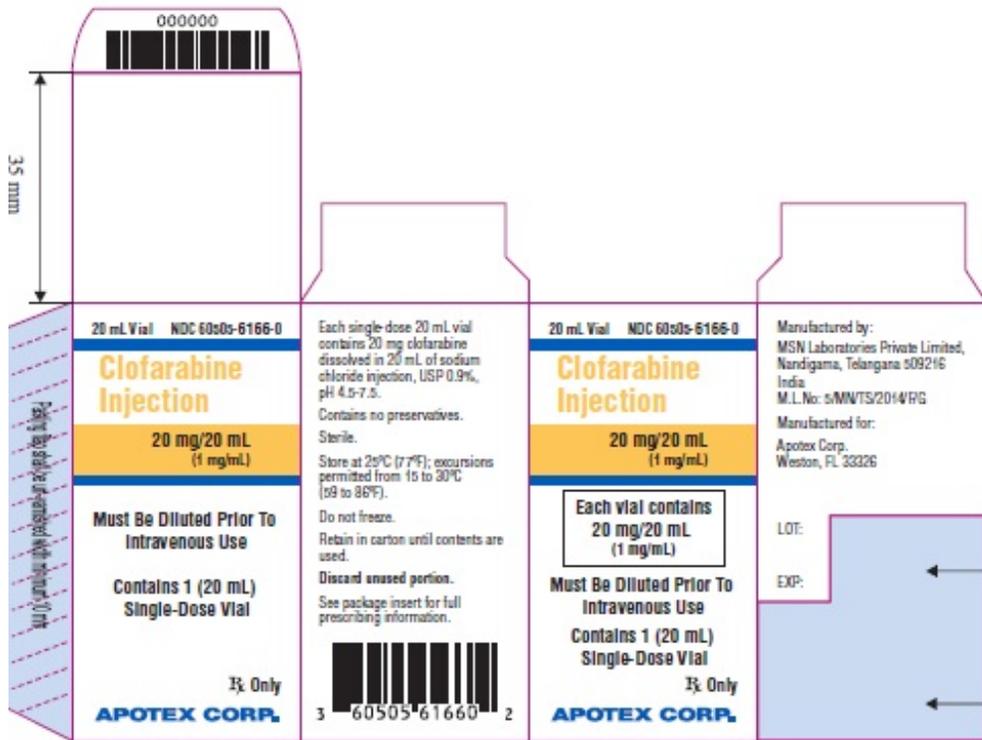
Each single-dose 20 mL vial contains 20 mg clofarabine dissolved in 20 mL of sodium chloride injection, USP 0.9%, pH 4.5-7.5.

Contains no preservatives.

Sterile.

Rx only

Apotex Corp.



Package Label - Principal Display Panel – 20 mL Single-Dose Vial

NDC 60505-6166-0

Clofarabine Injection

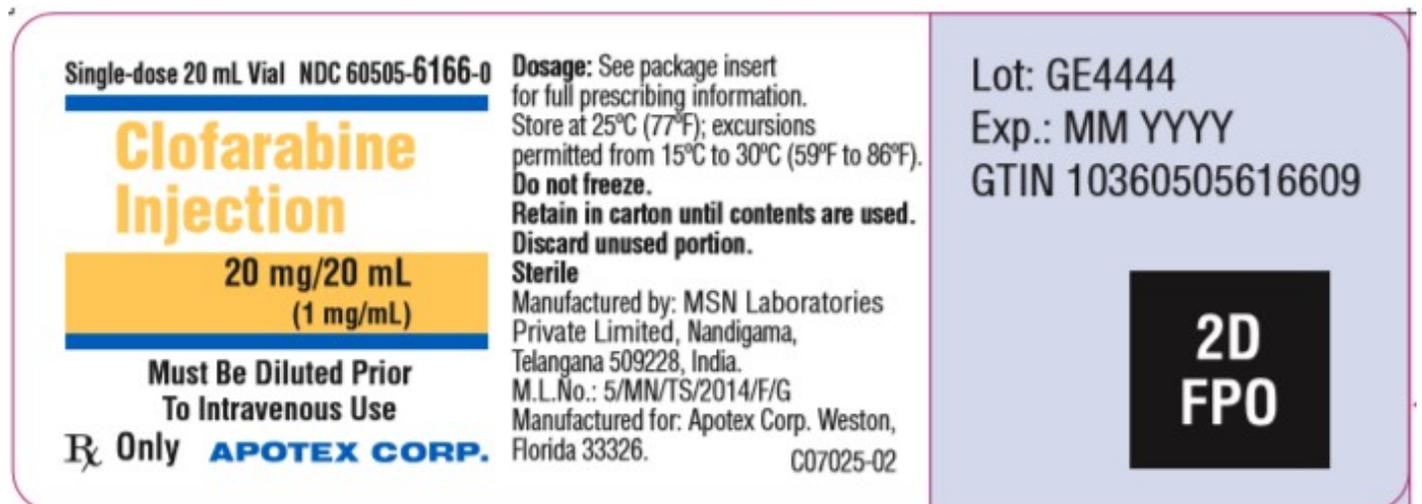
20 mg/20 mL (1 mg/mL)

Must Be Diluted Prior To Intravenous Use

Sterile

Rx only

Apotex Corp.



CLOFARABINE

clofarabine injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:60505-6166
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOFARABINE (UNII: 762RDY0Y2H) (CLOFARABINE - UNII:762RDY0Y2H)	CLOFARABINE	1 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	9 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60505-6166-0	1 in 1 CARTON	01/01/2018	
1		20 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209775	01/01/2018	

Labeler - Apotex Corp. (845263701)

Registrant - MSN Laboratories Private Limited (650786952)

Establishment

Name	Address	ID/FEI	Business Operations
MSN Laboratories Private Limited		650786952	manufacture(60505-6166) , analysis(60505-6166)

Establishment

Name	Address	ID/FEI	Business Operations
MSN Laboratories Private Limited		650534907	api manufacture(60505-6166)