HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Clolar® (clofarabine) Injection for intravenous use
Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions (5.2, 5.3, 5.10) 09/2014

INDICATIONS AND USAGE

Clolar® (clofarabine) injection is a purine 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 Clolar. (1)

DOSE 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, antihyperemic treatment, and alkalinization of urine throughout the 5 days of Clolar administration to reduce the risk of tumor lysis and other adverse events. (2.1)
• Discontinue Clolar if hypotension develops during the 5 days of administration. (2.1)
• Reduce the dose in patients with renal impairment. (2.1)
• Use dose modification for toxicity. (2.3)

DOSE FORMS AND STRENGTHS

• 20 mg/20 mL single-use vial. (3)

CONTRAINdications

• None. (4)

WARNINGS AND PRECAUTIONS

• Myelosuppression: May be severe and prolonged. Monitor complete blood counts and platelet counts during Clolar therapy. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 10%): nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-RX-CLOLAR or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

• Safety and effectiveness have not been established in adults. (8.6)
• Embryo-fetal Toxicity: fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Clolar. (5.8, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE

Clolar® (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 Clolar.

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. 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. To prevent drug incompatibilities, no other medications should be administered through the same intravenous line.

• Provide supportive care, such as intravenous fluids, antihyperemic treatment, and alkalinize urine throughout the 5 days of Clolar administration to reduce the effects of tumor lysis and other adverse events.
• Discontinue Clolar if hypotension develops during the 5 days of administration.
• Monitor renal and hepatic function during the 5 days of Clolar administration [see Warnings and Precautions (5.6, 5.7)].
• Monitor patients taking medications known to affect blood pressure. Monitor cardiac function during administration of Clolar.
• 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)].

2.2 Supportive Medications and Medications to Avoid

• Consider prophylactic anti-emetic medications as Clolar is moderately emetogenic.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

7. DRUG INTERACTIONS

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Adults with Hematologic Malignancies

8.7 Renal Impairment

8.8 Hepatic Impairment

9. OVERDOSE

10. DESCRIPTION

11. CLINICAL PHARMACOLOGY

12. NONCLINICAL TOXICOLOGY

13. CLINICAL STUDIES

14. REFERENCES

15. HOW SUPPLIED/STORAGE AND HANDLING

16. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
2.3 Dose Modifications and Reinitiation of Therapy

- Hematologic Toxicity
  - Administer subsequent cycles no sooner than 14 days from the starting day of the previous cycle and provided the patient’s ANC ≥ 0.75 × 10^9/L.
  - If a patient experiences a Grade 4 neutropenia (ANC <0.5 × 10^9/L) lasting 2-4 weeks, reduce dose by 25% for the next cycle.
- Non-hematologic Toxicity
  - Withhold Clolar if a patient develops a clinically significant infection, until the infection is controlled, then restart at the full dose.
  - Withhold Clolar for a Grade 3 non-hematologic toxicity (excluding transient elevations in serum transaminases and/or serum bilirubin and/or nausea/vomiting controlled by antiemetic therapy). Re-institute Clolar administration at a 25% dose reduction when resolution or return to baseline.
  - Discontinue Clolar administration for a Grade 4 non-hematologic toxicity.
  - Discontinue Clolar administration if a patient shows early signs or symptoms of SIRS or capillary leak (e.g., hypotension, tachycardia, tachypnea, and pulmonary edema) occur and provide appropriate supportive measures.
  - Discontinue Clolar administration if Grade 3 or higher increases in creatinine or bilirubin are noted. Re-institute Clolar 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.

2.4 Reconstitution/Preparation

Clolar should be filtered through a sterile 0.2 micron syringe filter and then diluted with 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, prior to intravenous (IV) infusion to a final concentration of 0.15 mg/mL. Use within 24 hours of preparation. Store diluted Clolar at room temperature (15–30°C).

2.5 Incompatibilities

Do not administer any other medications through the same intraveneous line.

3. DOSAGE FORMS AND STRENGTHS

20 mg/20 mL (1 mg/mL) single-use vial

4. CONTRAINDICATIONS

- None

5. WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Clolar 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 Clolar treatment and appears to be dose-dependent. Monitor complete blood counts [see Dosage and Administration (2.3)].

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

Clolar 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 Clolar treatment, including fungal, viral and bacterial infections. Monitor patients for signs and symptoms of infection, discontinue Clolar, and treat promptly.

5.4 Hyperuricemia (Tumor Lysis)

Administration of Clolar may result in tumor lysis syndrome associated with the break-down 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

Clolar 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 multi-organ failure. Close monitoring for this syndrome and early intervention may reduce the risk. Immediately discontinue Clolar and provide appropriate supportive measures. The use of prophylactic steroids (e.g., 100 mg/m^2) hydrocortisone on days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak. Consider use of diuretics and/or albumin. After the patient is stabilized and organ function has returned to baseline, re-treatment with Clolar 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/m^2) when used in combination with atosiposide (100 mg/m^2) and cyclophosphamide (440 mg/m^2). Severe hepatic events have been reported in a phase I/II clinical study of clofarabine in pediatric patients with relapsed or refractory acute leukemia. Two cases (2%) of VOD in the mono-therapy studies were reported. Clolar should be used with caution in pediatric patients with history of veno-occlusive disease of the liver following treatment with clofarabine. Enterocolitis may lead to necrosis, perforation, hemorrhage or sepsis complications. Monitor patients for signs and symptoms of enterocolitis and treat promptly [see Adverse Reactions (6.2)].

5.10 Skin Reactions

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

6. ADVERSE REACTIONS

The following 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) [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

Experience with Clolar is based on clinical studies conducted under varying treatment conditions with patients with relapsed or refractory Acute Lymphoblastic Leukemia (ALL) or Acute Myelogenous Leukemia (AML). In total, 115 pediatric patients treated in clinical trials received the recommended dose of Clolar 52 mg/m^2 daily × 5. The median number of cycles was 2. The median cumulative amount of Clolar received by pediatric patients during all cycles was 250 mg/m^2.

The most common adverse reactions occurring in 10% or more of patients treated with Clolar are:

- Nausea, vomiting, diarrhea, febrile neutropenia, headache, rash, pruritus, pyrexia, fatigue, palmar-plantar erythrodysesthesia syndrome, anxiety, flushing, and mucosal inflammation.

6.2 Adverse Reactions by System Organ Class

Table 1 lists adverse reactions by System Organ Class, including severe or life-threatening (NCI CTC Criteria Grade 3 or Grade 4), reported in ≥ 5% of the 115 patients in the 52 mg/m^2/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>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/Lymphatic System Disorders</td>
<td>Febrile neutropenia</td>
<td>63</td>
<td>55</td>
<td>59</td>
<td>51</td>
<td>51</td>
<td>3</td>
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<tr>
<td></td>
<td>Neutropenia</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Pericardial effusion</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain</td>
<td>40</td>
<td>35</td>
<td>8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>64</td>
<td>56</td>
<td>14</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gingival or mouth bleeding</td>
<td>20</td>
<td>17</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>84</td>
<td>73</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Oral mucosal petechiae</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proctalgia</td>
<td>9</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>90</td>
<td>78</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 1: Most Commonly Reported (≥ 5% Overall) Adverse Reactions by System Organ Class (N=115 pooled analysis) (continued)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term*</th>
<th>ALL/AML (N=115)</th>
<th>Worst NCI Common Terminology Criteria Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>12 10</td>
<td>1 1 1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Chills</td>
<td>39 34</td>
<td>3 3 3 3</td>
<td>. . . .</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 34</td>
<td>3 3 2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Irritability</td>
<td>11 10</td>
<td>1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>18 16</td>
<td>2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Edema</td>
<td>14 12</td>
<td>2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Pain</td>
<td>17 15</td>
<td>7 6 1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 39</td>
<td>16 14</td>
<td>. . . .</td>
</tr>
<tr>
<td>Hepatobiliary Disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>9 8</td>
<td>2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>10 9</td>
<td>10 9</td>
<td>. . . .</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>8 7</td>
<td>1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Catheter related infection</td>
<td>14 12</td>
<td>13 11</td>
<td>. . . .</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>9 8</td>
<td>7 6</td>
<td>. . . .</td>
</tr>
<tr>
<td>Clostridium colitis</td>
<td>8 7</td>
<td>6 5</td>
<td>. . . .</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>11 10</td>
<td>6 5</td>
<td>. . . .</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>8 7</td>
<td>6 5</td>
<td>. . . .</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>13 11</td>
<td>2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 10</td>
<td>6 5 1 1 1 1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Sepsis, including septic shock</td>
<td>19 17</td>
<td>6 5 4 4 9 8</td>
<td>. . . .</td>
</tr>
<tr>
<td>Staphylococcal bacteremia</td>
<td>7 6</td>
<td>5 4 1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Staphylococcal sepsis</td>
<td>6 5</td>
<td>5 4 1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 5</td>
<td>1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>34 30</td>
<td>6 5 8 7</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Arthralgia</td>
<td>10 9</td>
<td>3 3</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 10</td>
<td>3 3</td>
<td>. . . .</td>
</tr>
<tr>
<td>Bone pain</td>
<td>11 10</td>
<td>3 3</td>
<td>. . . .</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 14</td>
<td>.</td>
<td>. . . .</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>34 30</td>
<td>6 5</td>
<td>. . . .</td>
</tr>
<tr>
<td>Neoplasms, Benign, Malignant and Unspecified (incl. cysts and polyps)</td>
<td>Tumor lysis syndrome</td>
<td>7 6</td>
<td>7 6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>49 43</td>
<td>6 5</td>
</tr>
<tr>
<td>Lethargy</td>
<td>12 10</td>
<td>1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11 10</td>
<td>1 1</td>
<td>. . . .</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Agitation</td>
<td>6 5</td>
<td>1 1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24 21</td>
<td>2 2</td>
<td>. . . .</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Hematuria</td>
<td>15 13</td>
<td>2 2</td>
</tr>
</tbody>
</table>

### Table 2: Incidence of Treatment-Emergent Laboratory Abnormalities after Clolar Administration

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

### 6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Clolar. 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 Clolar.

- **Gastrointestinal disorders**: Gastrointestinal hemorrhage including fatalities.
- **Metabolism and nutrition disorders**: Hypoalimentation.
- **Skin and subcutaneous tissue 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 Clolar and other medications (e.g., allopurinol or antibiotics) known to cause these syndromes. Other exfoliative conditions have also been reported.
In a Phase 1 study of adults with refractory and/or relapsed hematologic malignancies, the recombinant clofarabine showed clastogenic 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).

Studies in adult patients treated with clofarabine 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/m²/day, approximately 17% of clinical recommended dose on a mg/m² basis). The testes of rats receiving 25 mg/kg/day (150 mg/m²/day, approximately 3 times the recommended clinical dose on a mg/m² basis) in a 4-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 0.575 mg/kg/day (7.5 mg/m²/day, approximately 14% of the clinical recommended dose on a mg/m² basis). Ovarian atrophy or degeneration and uterine mucosal atrophy were observed in female mice at 75 mg/kg/day (225 mg/m²/day, approximately 4-fold of recommended human dose on a mg/m² basis), the only dose administered to female mice. The effect on human fertility is unknown.

**8.3 Nursing Mothers**

No in-vivo drug interaction studies have been conducted [see Drug Interactions] (on a mg/m² basis), and in rabbits receiving a 12 mg/m²/day (approximately 23% of the recommended clinical dose on a mg/m² 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 risk to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with clofarabine. All patients should be advised to use effective contraceptive measures to prevent pregnancy.

**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 Clofar 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 Clofar 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.

**Drug-Drug Interactions**

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 66% and 140%, respectively, compared to patients with normal (N = 65) renal function (AUC, greater than 90 mL/min).

**8.8 Hepatic Impairment**

Clofar has not been studied in patients with hepatic impairment.

10. OVERDOSAGE

There were no known overdoses of Clofar. The highest daily dose administered to a human to date (on a mg/m² basis) has been 70 mg/m²×5 days (2 pediatric ALL patients). The toxicities included in these 2 patients included Grade 4 hyperbilirubinemia, Grade 2 and 3 vomiting, and Grade 3 neutropenia. In a Phase 1 study of adults with refractory or relapsed hematologic malignancies, the recommended pediatric dose of 52 mg/m²/day was not tolerated.

11. DESCRIPTION

Clofarabine (clofarabine) Injection contains clofarabine, a purine nucleoside metabolic inhibitor. Clofarabine (1 mg/mL) is supplied in a 20 mL, single-use vial. The 20 mL vial contains 20 mg clofarabine formulated in 20 mL unpreserved 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,1
dear, 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 deoxyribonucleoside kinases (dNKs), and to the 5-triphosphate metabolite by the purine nucleoside metabolism inhibitor, OAT3, and OCT1. A preclinical study using perfused rat kidney demonstrated that the renal excretion of clofarabine was decreased by cinetidine, an inhibitor of the hOCT2. Although the clinical implications of this finding have not been determined, extreme CaCl 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 stimulated clastogenic 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).

**14. CLINICAL STUDIES**

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

**Dose Escalation Study in Pediatric Patients with Hematologic Malignancies**

The safety and efficacy of Clofar were evaluated in pediatric patients with relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study. The starting dose of Clofar was 11.25 mg/m²/day IV infusion daily × 5 and escalated to 70 mg/m²/day IV infusion daily × 5. The dose schedule was then repeated every 2 to 6 weeks depending on toxicity and response. Nine of 17 ALL patients were treated with Clofar 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 (DLTs) in this study were reversible hyperbilirubinemia and elevated transaminase levels and anemia in a patient at 70 mg/m². A subsequent study at this dose level was not possible due to the toxicity risk associated with the dose. Complete remission (CR) rates in this study were 52 mg/m²/day for 5 days.

**Single-Arm Study in Pediatric ALL**

Clofar 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 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, 3861 (62%), had received ≥2 prior regimens and 1681 (30%) of the patients had received ≥3 prior regimens. 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 (≤5% blasts), and recovery of peripheral counts [platelets ≥ 100 × 10⁹/L and absolute neutrophil count (ANC) ≥ 1.0 × 10⁹/L]. CRp was defined as meeting all criteria for CR except for recovery of platelet counts to ≥ 100 × 10⁹/L. Partial Response (PR) was also defined, defined as complete disappearance of circulating blasts, an M0 bone marrow (≥5% and ≤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 uninformed 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**

| CR % [95% CI] | 11.5 (4.7, 22.2) |
| Cyp % [95% CI] | 8.2 (2.7, 18.1) |
| Median Duration of CR plus Cyp (range in weeks) | 10.7 (4.3 to 58.6) |

**CR = Complete response**

**Cyp = Complete response without platelet recovery**

*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 CR, 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**


**16. HOW SUPPLIED/STORAGE AND HANDLING**

Clofar (clofarabine) Injection is supplied in single-use vials containing 20 mg of clofarabine in 20 mL of solution. Each box contains 1 Clofar vial (NDC 0024-5860-51). The 20 mL vial contains approximately 3.6 mg/mL of solution. The pH range of the solution is 4.5 to 7.0. Vials containing undiluted Clofar should be stored at 25°C (77°F); excursions permitted to 15° – 30°C (59 – 86°F).

Diluted admixtures may be stored at room temperature, but must be used within 24 hours of preparation.
Procedures for proper handling and disposal should be utilized. Handling and disposal of Clolar should conform to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published.

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) and Adverse Reactions (6.1)].

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 (5.2) and Adverse Reactions (6.1)].

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 Clolar administration. Also, advise patients of the possibility of developing liver function abnormalities and to immediately report signs or symptoms of jaundice [see Warnings and Precautions (5.6) (5.7)].

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 (5.4) and Adverse Reactions (6.1)].

Pregnancy and Breast-feeding: Advise male and female patients with reproductive potential to use effective contraceptive measures to prevent pregnancy [see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]. Advise female patients to avoid breast-feeding during Clolar treatment [see Use in Specific Populations (8.3)].

Gastrointestinal Disorders: Advise patients that they may experience nausea, vomiting, and/or diarrhea with Clolar. If these symptoms are significant, they should seek medical attention.

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

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