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 (5.7) 12/2015
Warnings and Precautions (5.8) 10/2016

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 2 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, antihyperuricemic treatment, and alkalization 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)

DOSAGE FORMS AND STRENGTHS
• 20 mg/20 mL single-dose vial. (3)

CONTRAINDICATIONS
None. (4)

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)

WARNINGS AND PRECAUTIONS
• Myelosuppression: May be severe and prolonged. Monitor complete blood counts and platelet counts during Clolar therapy. (5.1)
• Hemorrhage: Serious and fatal cerebral, gastrointestinal and pulmonary hemorrhage. Monitor platelets and coagulation parameters and treat accordingly. (5.2)
• Infecions: Severe and fatal sepsis as a result of bone marrow suppression. Monitor for signs and symptoms of infection; discontinue Clolar 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 Clolar immediately if suspected. (5.5)
• Venous Occlusive Disease of the Liver: Monitor for and discontinue Clolar if suspected. (5.6)
• Hepatotoxicity: Severe and fatal hepatotoxicity. Monitor liver function, for signs and symptoms of hepatitis and hepatic failure. Discontinue Clolar 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 Clolar. (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)

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 Genzyme Corporation at 1-800-RX-CLOLAR or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
• Embryo-fetal Toxicity: fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Clolar. (5.11, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

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  2.1 Recommended Dosage
  2.2 Supportive Medications and Medications to Avoid
  2.3 Dose Modifications and Reinitiation of Therapy
  2.4 Reconstitution/Preparation
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3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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  5.5 Systemic Inflammatory Response Syndrome (SIRS) and Capillary Leak Syndrome
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FULL PRESCRIBING INFORMATION

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, antihyperuricemic treatment, and alkalize urine throughout the 5 days of Clolar administration to reduce the effects of tumor lysis and other adverse events.

2.2 Supportive Medications and Medications to Avoid
- Consider prophylactic anti-emetic medications as Clolar is moderately emetogenic.
- Minimize exposure to drugs with known renal toxicity during the 5 days of Clolar administration.
- Consider avoiding concomitant use of medications known to induce hepatic toxicity.
- Provide supportive care, such as intravenous fluids, antihyperuricemic treatment, and alkalinize urine throughout the 5 days of Clolar administration to reduce the effects of tumor lysis and other adverse events.

2.3 Dose Modifications and Reinitiation of Therapy
- Discontinue Clolar if hypotension develops during the 5 days of administration.
- Monitor renal and hepatic function during the 5 days of Clolar administration.
- Use dose modification for toxicity.
- Reduce the dose in patients with renal impairment.

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

2.5 Incompatibilities
- There is insufficient information to make a dosage recommendation in patients with CrCL less than 30 mL/min.
- Monitor for signs and symptoms of infection; discontinue Clolar and treat promptly.
- Discontinue Clolar immediately if suspected.
- 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.

3 DOSAGE FORMS AND STRENGTHS
- 20 mg/20 mL single-dose vial.

4 CONTRAINDICATIONS
- None.

5 WARNINGS AND PRECAUTIONS
- Myelosuppression: May be severe and prolonged. Monitor complete blood counts and platelet counts during Clolar therapy.
- Hemorrhage: Serious and fatal cerebral, gastrointestinal and pulmonary hemorrhage. Monitor platelets and coagulation parameters and treat accordingly.
- Infections: Severe and fatal sepsis as a result of bone marrow suppression. Monitor for signs and symptoms of infection; discontinue Clolar and treat promptly.
- Tumor Lysis Syndrome: Anticipate, monitor for signs and symptoms and treat promptly.
- Systemic Inflammatory Response Syndrome (SIRS) or Capillary Leak Syndrome: Monitor for and discontinue Clolar immediately if suspected.
- Venous Occlusive Disease of the Liver: Monitor for and discontinue Clolar if suspected.
- Hepatotoxicity: Severe and fatal hepatotoxicity. Monitor liver function, for signs and symptoms of hepatitis and hepatic failure. Discontinue Clolar immediately for Grade 3 or greater liver enzyme and/or bilirubin elevations.
- Renal Toxicity: Increased creatinine and acute renal failure; monitor renal function and interrupt or discontinue Clolar.
- 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.
- 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.

6 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.

7 USE IN SPECIFIC POPULATIONS
- Embryo-fetal Toxicity: fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Clolar.

8 OVERDOSAGE
- Discontinue Clolar if hypotension develops during the 5 days of administration.
- Monitor renal and hepatic function during the 5 days of Clolar administration.
- 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.

9 DESCRIPTION
- 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.

10 CLINICAL PHARMACOLOGY
- Mechanism of Action
- Pharmacokinetics

11 NONCLINICAL TOXICOLOGY
- Carcinogenesis, Mutagenesis, Impairment of Fertility

12 CLINICAL STUDIES

13 REFERENCES

14 HOW SUPPLIED/STORAGE AND HANDLING

15 PATIENT COUNSELING INFORMATION
- *Sections or subsections omitted from the full prescribing information are not listed*

Revised: 10/2016
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 is ≥0.75 × 10^9/L.
  - If a patient experiences a Grade 4 neutropenia (ANC <0.5 × 10^9/L) lasting ≥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-infectious 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-infectious 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 Preparation/Reconstitution

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 between 0.15 mg/mL and 0.4 mg/mL. 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 intravenous line.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg/mL (1 mL per dose, single-dose 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 platelet 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 breakdown of 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 medications 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. Close monitoring for this syndrome and early intervention may reduce the risk of mortality. Immediately discontinue Clolar and provide appropriate supportive measures. The use of prophylactic steroids (e.g., 100 mg/m²/day dose by 25% from 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/m²) when used in combination with etoposide (100 mg/m²) and cyclophosphamide (440 mg/m²). Severe hepatotoxicity has been reported in a combined study of clofarabine in pediatric patients with relapsed or refractory 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 Clolar 52 mg/m² daily × 5. The median number of cycles was 2. The median cumulative amount of Clolar received by pediatric patients during all cycles was 540 mg.

5.7 Hepatotoxicity

- Severe and fatal hepatotoxicity, including hepatic and hepatic failure, has occurred with the use of Clolar [see Adverse Reactions (6.2)]. In clinical studies, Grade 3–4 liver enzyme elevations were observed in pediatric patients during treatment with Clolar at the following rates: elevated aspartate aminotransferase (AST) occurred in 36% of patients, elevated alanine aminotransferase (ALT) occurred in 44% of patients, Grade 3 ALT and AST elevations typically occurred within 10 days of Clolar 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 multi-organ 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 multi-organ failure. Monitor hepatic function and for signs and symptoms of hepatitis and hepatic failure. Discontinue Clolar immediately for Grade 3 or greater liver enzyme and/or bilirubin elevations [see Warnings and Precautions (5.3)].

5.8 Renal Toxicity

Clolar may cause acute renal failure. In Clolar 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 Clolar. Hematuria occurred in 13% of Clolar treated patients overall. Monitor patients for renal toxicity and interrupt or discontinue Clolar as necessary [see Adverse Reactions (6.1)].

5.9 Enterocolitis

Fatal and serious cases of enterocolitis, including neutropenic colitis, cecitis, and C. difficile colitis, have been observed 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 [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

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 Clolar in 115 pediatric patients with relapsed or refractory 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 Clolar 52 mg/m² daily × 5. The median number of cycles was 2. The median cumulative amount of Clolar 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 CTC Grade 3 or Grade 4), reported in ≥25% 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>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>N %</th>
<th>N %</th>
<th>N %</th>
<th>N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Febrile neutropenia</td>
<td>63</td>
<td>55</td>
<td>59</td>
<td>51</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Neutropenia</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Tachycardia</td>
<td>40</td>
<td>35</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

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 CTC Grade 3 or Grade 4), reported in ≥25% 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) (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>3</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</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>39 34</td>
<td>3 3</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 34</td>
<td>3 3</td>
<td>2</td>
</tr>
<tr>
<td>Irritability</td>
<td>11 10</td>
<td>1 1</td>
<td>.</td>
</tr>
<tr>
<td>Musculoskeletal inflammation</td>
<td>16 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</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 39</td>
<td>16 14</td>
<td>.</td>
</tr>
<tr>
<td>Hepatobiliary Disorder</td>
<td>Jaundice</td>
<td>9 8 2</td>
<td>2</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Bacteriaemia</td>
<td>10 9</td>
<td>8 9</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>8 7 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Catheter related infection</td>
<td>14 12 13</td>
<td>7 11</td>
<td>7</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>9 8 7</td>
<td>6</td>
<td>.</td>
</tr>
<tr>
<td>Clostridum colitis</td>
<td>8 7 6</td>
<td>5</td>
<td>.</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>11 10 6</td>
<td>5</td>
<td>.</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>8 7 6 5</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>13 11 2</td>
<td>2</td>
<td>.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 10 6 5</td>
<td>1 1</td>
<td>1 1</td>
</tr>
<tr>
<td>Sepsis, including septic shock</td>
<td>19 17 6 5</td>
<td>4 4 9</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcal bacteremia</td>
<td>7 6</td>
<td>5 4</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcal sepsis</td>
<td>6 5 5</td>
<td>4 1</td>
<td>1</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</td>
<td>30 6 5</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 6</td>
<td>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</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>

*Patients with more than one preferred term within a SOC are counted only once in the SOC totals. Patients with more than one occurrence of the same preferred term are counted only once within that term and at the highest severity grade.

The following less common adverse reactions have been reported in 1–4% 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, gastrointestinal adenovirus, infection, influenza, parainfluenza virus infection, pneumonia fungal, pneumonia primary atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection
- Investigations: blood creatinine increased
- Metabolism and Nutrition Disorders: hyperglycemia
- Psychiatric Disorders: mental status change
- Respiratory, Thoracic and Mediastinal Disorder: pulmonary edema

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

**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</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>88%</td>
<td>88%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64%</td>
<td>64%</td>
</tr>
<tr>
<td>Thrombocytopenia</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 Postmarketing 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: hypoglycemia
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) (including fatal cases)
In a Phase 1 study of adults with refractory and/or relapsed hematologic malignancies, the recom-
maculopapular rash. These 2 patients included Grade 4 hyperbilirubinemia, Grade 2 and 3 vomiting, and Grade 3
epididymal and degeneration of the seminiferous epithelium in the testes were observed in dogs receiving 2.375 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 apoptosis 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
in the bacterial mutation assay (Ames test).

14 CLINICAL STUDIES

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

Dose Escalation Study in Pediatric Patients with Hematologic Malignancies

The safety and efficacy of Clolar were evaluated in pediatric patients with refractory or relapsed hematologic malignancies in an open-label, dose-escalation, noncomparative study. The starting dose of
Clolar was 11.5 mg/m²/day IV infusion daily x 5 and escalated to 73 mg/m²/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 Clolar 52 mg/m²/day for 5 days. In the 17 ALL patients there
were 2 complete remissions (12%) and 2 partial remissions (12%) at varying doses. Dose-limiting
toxicity (DLT) in this study was 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

Clolar 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. Median
response rate of 38/61 (62%), 13/61 (21%), and 3/61 (5%) of the patients had achieved CR, CRp, and CR
respectively. Of the 13 patients who achieved CR, 12/13 (92%) had received >2 prior regimens and 18/20 (90%)
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 (≤5% blasts), and recovery of peripheral counts (Platelets ≥100 x 10^9/L
and absolute neutrophil count [ANC] ≥1.0 x 10^9/L). CRp was defined as meeting all criteria for CR
except for recovery of platelet counts to ≥100 x 10^9/L. Partial Response (PR) was also determined,
defined as complete disappearance of circulating blasts, an M2 bone marrow (≤5% 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 Review Response 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 29–2,615 mg) in 1 (41%),(n=1) or
more patients. The recommendations for 3 or more (15%) cycles at 52 mg/m²/day for 2 pediatric ALL
patients was 2 (range 1–2). The median time between cycles was 28 days with a range of 12 to 55 days.

Table 3: Results in Single-Arm Pediatric ALL

<table>
<thead>
<tr>
<th>CR% [5% CI]</th>
<th>CRp% [5% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5 (4.7, 22.2)</td>
<td>8.2 (2.7, 18.1)</td>
</tr>
</tbody>
</table>

Median Duration of CR (plus CRp) (range in weeks) 10.7 (4.3 to 58.6)

CR = Complete response
CRp = 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 CR; the clinical relevance of a CR in this setting is unknown.
Of 35 patients who were refractory to their immediately preceding induction regimen, 6 (17%) achieved
CR or CRp. Of 19 patients who had at least 1 prior hematopoietic stem cell transplant (HSCT), 5
(26%) 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.

References


16 HOW SUPPLIED/STORAGE AND HANDLING

Clolar (clofarabine) Injection is supplied in single-dose flint vials containing 20 mg of clofarabine in 20
mL of solution. Each box contains 1 Clolar vial (NDC 0034-9860-01). The 20mL vials contain 20
mg (20 mL) of solution. The pH range of the solution is 4.5 to 7.5.

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

Drug metabolites may be stored at room temperature, but must be used within 24 hours
of preparation.

Preparations 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.11
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), 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 (5.3), 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. Advise patients of the signs or symptoms of 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), Adverse Reactions (6.1)].

Pregnancy and Breastfeeding: Advise male and female patients with reproductive potential to use effective contraceptive measures to prevent pregnancy [see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]. Advise female patients to avoid breastfeeding 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 [see Warnings and Precautions (5.9)].

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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