Administer the recommended pediatric dose of 52 mg/m² as an intravenous infusion over 2 hours daily for 5 consecutive days. Repeat cycles every 2–6 weeks. (2.1)

Provide supportive care, such as intravenous infusion fluids, antihyperuricemic treatment, and alkalinization of urine throughout the 5 days of clofarabine administration to reduce the risk of tumor lysis and other adverse events. (2.1)

Discontinue clofarabine 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)

When reducing the dose, reduce by 50% for a single dose, then reduce by 25% for each subsequent dose. (2.3)

Discontinue clofarabine 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)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

Most common adverse reactions (≥25%): vomiting, nausea, diarrhea, febrile neutropenia, pneumonia, 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 sanofi-aventis U.S. LLC at 1-800-633-1610 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 clofarabine. (5.11, 8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2016
Monitor patients taking medications known to affect blood pressure. Monitor cardiac
d function during administration of clofarabine.
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 clofarabine is moderately emeti-
genic.
Consider the use of prophylactic steroids to mitigate Systemic Inflammatory Re-
sponse Syndrome (SIRS) or capillary leak syndrome (e.g., hypertension, tachycardia,
tachypnea, and pulmonary edema).
Minimize exposure to drugs with known renal toxicity during the 5 days of clofarabine
administration since the risk of renal toxicity may be increased.
Consider avoiding concurrent use of medications known to induce hepatic toxicity.

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 >2
weeks, reduce dose by 25% for the next cycle.

Non-hematologic Toxicity
Withhold clofarabine if a patient develops a clinically significant infection, until the
infection is controlled, then restart at the full dose.
Withhold clofarabine 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 administration at a 25% dose reduction
when resolution or return to baseline.
Discontinue clofarabine administration for a Grade 4 non-infectious non-hema-
tologic toxicity.
Discontinue clofarabine administration if a patient shows early signs or symptoms
of SIRS or capillary leak (e.g., hypertension, tachycardia, tachypnea, and pulmo-
nary edema) occur and provide appropriate supportive measures.
Discontinue clofarabine administration if Grade 3 or higher increases in creatinine
or bilirubin are noted. Re-institute clofarabine 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
Clofarabine 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. Use
within 24 hours of preparation. Store diluted clofarabine 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/20 mL (1 mg/mL) single-dose vial

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
Clofarabine 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 hematologic toxicity (excluding manifestations of SIRS). Melphalan-induced SIRS was
usually reversible with interruption of clofarabine 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 hem-
orrhage, has occurred. The majority of the cases were associated with thrombocytopenia.
Monitor platelets and coagulation parameters and treat according [see Adverse Reac-
tions (6.2)].

5.3 Infections
Clofarabine 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 93% of patients experienced at least one infection after
clofarabine treatment, including fungal, viral and bacterial infections. Monitor patients for
signs and symptoms of infection, discontinue clofarabine, and treat promptly.

5.4 Hyperuricemia (Tumor Lysis)
Administration of clofarabine may result in tumor lysis syndrome associated with
the breakdown of 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 may cause a cytokine release syndrome (e.g., tachycardia, tachypnea,
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 with high-risk conditions (SIRS) and capillary leak syndrome.
Consider use of diuretics and/or albumin. After the patient is stabilized and organ function
has returned to baseline, re-treatment with clofarabine 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]) or used in combination with etoposide ([100 mg/m²]) and
cyclophosphamide ([440 mg/m²]). Severe hepatic toxic 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 mono-therapy studies were considered related
to study drug. Monitor for and discontinue clofarabine if VOD is suspected.

5.7 Hepatotoxicity
Severe and fatal hepatotoxicity, including hepatitis and hepatic failure, has occurred with
the use of clofarabine [see Adverse Reactions (6.2)]. In clinical studies, Grade 3-4 liver
enzyme elevations were observed in pediatric patients during treatment with clofarabine
at the following rates: elevated aspartate aminotransferase (AST) occurred in 36% of
patients; elevated alanine aminotransferase (ALT) occurred in 44% of patients. ALT
and AST elevations typically occurred within 10 days of clofarabine 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 (hepatic bilirubinemia 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 signs for symptoms of hepatitis and hepatic failure. Discontinue clofarabine immediately for Grade 3 or greater liver enzyme and/or bilirubin elevations [see Adverse Reactions (6.1)].

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)]
Enteroctis [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
events 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 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 52 mg/m² daily × 5. The median number of cycles was 2. The median cumulative amount of clofarabine 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,
myalgia, diaphoresis, increased in extraneous, hypertension, constipation.

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)

<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>51</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Worst NCI Common Terminology Criteria Grade

<table>
<thead>
<tr>
<th>System</th>
<th>ALL/AML</th>
<th>N=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
<td>**</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&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>9 8</td>
<td>0.1 1</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>40 35</td>
<td>6 5</td>
<td>.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40 35</td>
<td>8 7</td>
<td>.</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>9 8</td>
<td>1 1</td>
<td>.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>64 56</td>
<td>14 12</td>
<td>.</td>
</tr>
<tr>
<td>Gingival or mouth bleeding</td>
<td>20 17</td>
<td>8 7 1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>84 73</td>
<td>16 14 1</td>
<td>1</td>
</tr>
<tr>
<td>Oral mucosal petechiae</td>
<td>6 5</td>
<td>4 4</td>
<td>.</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>9 8</td>
<td>2 2</td>
<td>.</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 7</td>
<td>1 1</td>
<td>.</td>
</tr>
<tr>
<td>Vomiting</td>
<td>90 78</td>
<td>9 8</td>
<td>1 1</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>.</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</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 39</td>
<td>16 14</td>
<td>.</td>
</tr>
<tr>
<td>Jaundice</td>
<td>9 8</td>
<td>2 2</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</td>
<td>1</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</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>Anorexia</td>
<td>34 30</td>
<td>6 5 8 7</td>
<td>.</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 9</td>
<td>3 3</td>
<td>.</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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>N % N % N % N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)</td>
<td>Tumor lysis syndrome</td>
<td>7 6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>49 43</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>12 10</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>11 10</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Agitation</td>
<td>6 5</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>24 21</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Hematuria</td>
<td>15 13</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Dyspnea</td>
<td>15 13</td>
</tr>
<tr>
<td></td>
<td>Epitaxis</td>
<td>31 27</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td>14 12</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>12 10</td>
</tr>
<tr>
<td></td>
<td>Tachypnea</td>
<td>10 9</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Erythema</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Palmar-plantar erythrodynesthesia syndrome</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Rash pruritic</td>
<td>9</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Flushing</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>33</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, gastroenteritis adenovirus, infection, influenza, parainfluenza virus infection, pneumonia fungal, pneumonia primary atypical, Respiratory syncytial virus infection, sinusitis, staphylococcal infection
- Psychiatric Disorders: mental status change
- Respiratory, Thoracic and Mediastinal Disorder: pulmonary edema

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

12.1 Pharmacokinetics

The population pharmacokinetics of clofarabine 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/m\(^2\) dose, similar concentrations were observed over a 24-hour urine collection (41% [17%] of the recommended clinical dose on a mg/m\(^2\) basis). The testes of rats receiving 25 mg/kg/day (150 mg/m\(^2\) daily, approximately 3 times the recommended clinical dose on a mg/m\(^2\) basis) in a 6-month IV study did not show any evidence of testicular atrophy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice, rats, and dogs have demonstrated dose-related adverse effects on male reproductive organs. Seminiferous tubule and testicular degeneration and atrophy were reported in male mice receiving intraperitoneal (IP) doses of 3 mg/kg/day (9 mg/m\(^2\) daily) and 7 mg/kg/day (21 mg/m\(^2\) daily) of clofarabine. In male mice at 75 mg/kg/day (225 mg/m\(^2\) daily, approximately 4-fold of recommended human dose on a mg/m\(^2\) basis), the only dose administered to female mice. The effect on human fertility is unknown.

13.2 Impairment of Fertility

There are no adequate and well-controlled studies in pregnant women using clofarabine. Because these reactions are reported voluntarily from a population of patients treated with clofarabine, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In a Phase 1 study of adult patients with relapsed or refractory acute lymphoblastic leukemia, the highest daily dose administered to the pediatric studies, 49–60% of the dose is excreted in the urine unchanged. In vitro studies using isolated human hepatocytes indicate very limited metabolism (0.2%). The pathways of non-hepatic elimination remain unknown. Clofarabine has not been studied in patients with hepatic impairment.

Drug Interactions in vitro studies suggested that clofarabine undergoes limited metabolism and does not inhibit or induce major CYP enzymes. CYP inducers and inhibitors are unlikely to affect the metabolism of clofarabine. Clofarabine is unlikely to affect the metabolism of CYP substrates. However, 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 OCT2. Although the clinical implications of this finding have not been determined, signs of clofarabine toxicity should be monitored when administered with other drugs.

13.3 Nursing Mothers

It is not known whether clofarabine or its metabolites are excreted in human milk. Because these reactions are reported voluntarily from a population of patients treated with clofarabine, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

13.4 Pediatric Use

Children have not been systematically studied for the pharmacokinetics of clofarabine. 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).

13.5 Geriatric Use

Safety and effectiveness have not been established in adults.

13.6 Adults with Hematologic Malignancies

Safety and effectiveness have not been established in adults.

13.7 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.

13.8 Drug Interactions

There are no adequate and well-controlled studies in pregnant women using clofarabine. Because these reactions are reported voluntarily from a population of patients treated with clofarabine, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

13.9 Breastfeeding

There are no adequate and well-controlled studies in pregnant women using clofarabine. Because these reactions are reported voluntarily from a population of patients treated with clofarabine, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

14 CLINICAL STUDIES

14.1 Pediatric Studies

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

14.2 Single-Arm Study in Pediatric ALL

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

14.3 Phase 1 Study in Pediatric ALL

There were no known overdoses of clofarabine. The highest daily dose administered to a human to date (on a mg/m\(^2\) basis) has been 70 mg/m\(^2\)/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.

14.4 Phase 2 Study in Pediatric ALL

In a Phase 1 study of adult patients with refractory or relapsed hematologic malignancies, the recommended pediatric dose of 52 mg/m\(^2\)/day was not tolerated.

14.5 Phase 2 Study in Pediatric AML

Seventy-eight (78) pediatric patients with ALL were exposed to clofarabine. Seventy (70) of the patients received the recommended pediatric dose of clofarabine 52 mg/m\(^2\) daily for 5 days as an intravenous (IV) infusion.

14.6 Phase 2 Study in Pediatric MDS

There were no known overdoses of clofarabine. The highest daily dose administered to a human to date (on a mg/m\(^2\) basis) has been 70 mg/m\(^2\)/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.

14.7 Phase 2 Study in Pediatric MDS

In a Phase 1 study of adult patients with refractory or relapsed hematologic malignancies, the recommended pediatric dose of 52 mg/m\(^2\)/day was not tolerated.

14.8 Phase 2 Study in Pediatric AML

Response Review Panel (IRRP).
Table 3: Results in Single-Arm Pediatric ALL

<table>
<thead>
<tr>
<th>N=61</th>
<th>CR % [95% CI]</th>
<th>CRp % [95% CI]</th>
<th>Median Duration of CR plus CRp (range in weeks)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11.5 (4.7, 22.2)</td>
<td>8.2 (2.7, 18.1)</td>
<td>10.7 (4.3 to 58.6)</td>
</tr>
</tbody>
</table>

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 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

16 HOW SUPPLIED/STORAGE AND HANDLING
Clofarabine Injection is supplied in single-dose flint vials containing 20 mg of clofarabine in 20 mL of solution. Each box contains one clofarabine vial (NDC 0955-1746-01). The 20mL flint vials contain 20 mL (20 mg) of solution. The pH range of the solution is 4.5 to 7.5.

Vials containing undiluted clofarabine 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 clofarabine should conform to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published. 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), 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 clofarabine 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 (5.2), 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 clofarabine treatment [see Use in Specific Populations (8.3)].

Gastrointestinal Disorders: Advise patients that they may experience nausea, vomiting, and/or diarrhea with clofarabine. 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. If this symptom is significant, they should seek medical attention.

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