INDICATIONS AND USAGE

Acetadote is an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen (1)

The total dose of Acetadote is 300 mg/kg given as 3 separate doses and administered over a total of 21 hrs. Please refer to the guidelines below for dose preparation based upon patient weight.

Dosing for patients who weigh 5 kg to 20 kg (2.1):

Loading Dose: 150 mg/kg diluted in 3 mL/kg of diluent* administered over 1 hr
Second Dose: 50 mg/kg diluted in 7 mL/kg of diluent* administered over 4 hrs
Third Dose: 100 mg/kg diluted in 14 mL/kg of diluent* administered over 16 hrs

Dosing for patients who weigh 21 kg to 40 kg (2.1):

Loading Dose: 150 mg/kg diluted in 100 mL of diluent* administered over 1 hr
Second Dose: 50 mg/kg diluted in 250 mL of diluent* administered over 4 hrs
Third Dose: 100 mg/kg diluted in 500 mL of diluent* administered over 16 hrs

Dosing for patients who weigh 41 kg to 100 kg (2.1):

Loading Dose: 150 mg/kg diluted in 200 mL of diluent* administered over 1 hr
Second Dose: 50 mg/kg diluted in 500 mL of diluent* administered over 4 hrs
Third Dose: 100 mg/kg diluted in 1000 mL of diluent* administered over 16 hrs

*Acetadote is compatible with the following diluents; 5% Dextrose in Water, 0.45% Sodium Chloride Injection, and Sterile Water for Injection

No drug-drug interaction studies have been conducted (7)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-877-484-2700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: This drug should be used during pregnancy only if clearly needed (8.1)

Nursing Mothers: Unknown if drug is excreted in human milk (8.3)

Pediatric Use: See dose adjustment for patients less than 40 kg (2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: June/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Acetaminophen Assays Interpretation and Methodology – Acute Ingestion
1.2 Acetaminophen Assays Interpretation and Methodology – Repeated Supratherapeutic Ingestion

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions (Three-Bag Method: Loading, Second and Third dose)
2.2 Volume Adjustment: Patients less than 40 kg and Requiring Fluid Restriction
2.3 Renal Impairment
2.4 Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.3 Nursing mothers
8.4 Pediatric use
8.5 Geriatric use

10 OVERDOSE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of action
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Acetadote is an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen. Overdose incidences are divided into two types; Acute Ingestion or Repeated Supratherapeutic Ingestion (RSI). [see Dosage and Administration (2) and Acetaminophen Assays – Interpretation and Methodology-(Acute or Repeated Supratherapeutic Ingestion) (1.1, 1.2)].

On admission for suspected acute acetaminophen overdose, a serum blood sample should be drawn at least 4 hours after ingestion to determine the acetaminophen level and will serve as a basis for determining the need for treatment with acetylcysteine. If the patient presents after 4 hours post-ingestion, the serum acetaminophen sample should be determined immediately.

Acetadote should be administered within 8 hours from acetaminophen ingestion for maximal protection against hepatic injury for patients whose serum acetaminophen levels fall above the “possible” toxicity line on the Rumack-Matthew nomogram (line connecting 150 mcg/mL at 4 hours with 37.5 mcg/mL at 12 hours); [see Acetaminophen Assays – Interpretation and Methodology (1.1, 1.2)]. If the time of ingestion is unknown, or the serum acetaminophen level is not available, cannot be interpreted, or is not available within the 8 hour time interval from acetaminophen ingestion, Acetadote should be administered immediately if 24 hours or less have elapsed from the reported time of ingestion of an overdose of acetaminophen, regardless of the quantity reported to have been ingested.

The aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), bilirubin, prothrombin time, creatinine, blood urea nitrogen (BUN), blood glucose, and electrolytes also should be determined in order to monitor hepatic and renal function and electrolyte and fluid balance.

NOTE: The critical ingestion-treatment interval for maximal protection against severe hepatic injury is between 0 – 8 hours. Efficacy diminishes progressively after 8 hours and treatment initiation between 15 and 24 hours post-ingestion of acetaminophen yields limited efficacy. However, it does not appear to worsen the condition of patients and it should not be withheld, since the reported time of ingestion may not be correct.

1.1 Acetaminophen Assays Interpretation and Methodology – Acute Ingestion

The acute ingestion of acetaminophen in quantities of 150 mg/kg or greater may result in hepatic toxicity. However, the reported history of the quantity of a drug ingested as an overdose is often inaccurate and is not a reliable guide to therapy of the overdose. Therefore, plasma or serum acetaminophen concentrations, determined as early as possible, but no sooner than four hours following an acute overdose, are essential in assessing the potential risk of hepatotoxicity. If an assay for acetaminophen cannot be obtained, it is necessary to assume that the overdose is potentially toxic.

Interpretation of Acetaminophen Assays
1. When results of the plasma acetaminophen assay are available, refer to the nomogram in Figure 1 to determine if plasma concentration is in the potentially toxic range. Values above the line connecting 200 mcg/mL at 4 hours with 50 mcg/mL at 12 hours (probable line) are associated with a probability of hepatic toxicity if an antidote is not administered.
2. If the predetoxy plasma level is above the line connecting 150 mcg/mL at 4 hours with 37.5 mcg/mL at 12 hours (possible line), continue with maintenance doses of acetylcysteine. It is better to err on the safe side and thus this line, defining possible toxicity, is plotted 25% below the line defining probable toxicity.
3. If the predetoxy plasma level is below the line connecting 150 mcg/mL at 4 hours with 37.5 mcg/mL at 12 hours (possible line), there is minimal risk of hepatic toxicity, and acetylcysteine treatment may be discontinued.

Estimating Potential for Hepatotoxicity: The following depiction of the Rumack-Matthew nomogram has been developed to estimate the probability that plasma levels in relation to intervals post-ingestion will result in hepatotoxicity.

The Rumack-Matthew nomogram may underestimate the risk for hepatotoxicity in some patients with risk factors such as chronic alcoholism, malnutrition, or CYP2E1 enzyme inducing drugs (e.g., isoniazid).

Figure 1. Rumack-Matthew Nomogram

![Rumack-Matthew Nomogram](image-url)
1.2 Acetaminophen Assays Interpretation and Methodology – Repeated Supratherapeutic Ingestion

Repeated Supratherapeutic Ingestion (RSI) is defined as ingestion of acetaminophen at doses higher than those recommended for extended periods of time. The nomogram does not apply to patients with RSI. Treatment is based on the acetaminophen and elevated AST/ALT levels indicative of potential toxicity due to acetaminophen. For specific treatment information regarding the clinical management of repeated supratherapeutic acetaminophen overdose, please contact your regional poison center at 1-800-222-1222, or alternatively, a special health professional assistance line for acetaminophen overdose at 1-800-525-6115.

Figure 2. Acetadote Treatment Flow Chart

![Acetadote Treatment Flow Chart](image)

- Estimate time of acetaminophen ingestion
  - Less than 24 hrs since overdose
    - Draw serum for acetaminophen level at 4 hrs post-ingestion or as soon as possible thereafter
      - Plot level on nomogram
  - If time of ingestion is unknown or patient is considered unreliable, consider empiric initiation of acetylcysteine treatment
    - Plasma level plots below treatment line
    - Plasma level plots above treatment line
    - Stop acetylcysteine if initiated earlier
    - Administer acetylcysteine

1Acetaminophen levels drawn less than 4 hours post-ingestion may be misleading.
2With an extended-release preparation, an acetaminophen level drawn less than 8 hours post-ingestion may be misleading. Draw a second level at 4 to 6 hours after the initial level. If either falls above the toxicity line, acetylcysteine treatment should be initiated.
3Acetylcysteine may be withheld until acetaminophen assay results are available as long as initiation of treatment is not delayed beyond 8 hours post-ingestion. If more than 8 hours post-ingestion, start acetylcysteine treatment immediately.

2 DOSAGE AND ADMINISTRATION
The total dose of Acetadote is 300 mg/kg given as 3 separate doses and administered over a total of 21 hours. Please refer to the guidelines below for dose preparation based upon patient weight. The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction (see Tables 1 and 2).

2.1 Administration Instructions (Three-Bag Method: Loading, Second and Third Dose)

Dosing for Patients who weigh 5 kg to 20 kg (Table 1):

- **Loading Dose**: 150 mg/kg diluted in 3 mL/kg of diluent* administered over 1 hr
- **Second Dose**: 50 mg/kg diluted in 7 mL/kg of diluent* administered over 4 hrs
- **Third Dose**: 100 mg/kg diluted in 14 mL/kg of diluent* administered over 16 hrs

Table 1. Three Bag Method Dosage Guide by Weight in Patients 5 kg to 20 kg

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Bag 1 (loading dose): 150 mg/kg in 3 mL/kg of diluent* infused over 1 hour</th>
<th>Bag 2 (second dose): 50 mg/kg in 7 mL/kg of diluent* infused over 4 hours</th>
<th>Bag 3 (third dose): 100 mg/kg in 14 mL/kg of diluent* infused over 16 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acetadote Total Dose (mg)</td>
<td>Diluent volume (mL)</td>
<td>Acetadote Total Dose (mg)</td>
</tr>
<tr>
<td>5 kg</td>
<td>750 mg</td>
<td>15 mL</td>
<td>250 mg</td>
</tr>
<tr>
<td>10 kg</td>
<td>1,500 mg</td>
<td>30 mL</td>
<td>500 mg</td>
</tr>
<tr>
<td>15 kg</td>
<td>2,250 mg</td>
<td>45 mL</td>
<td>750 mg</td>
</tr>
<tr>
<td>20 kg</td>
<td>3,000 mg</td>
<td>60 mL</td>
<td>1,000 mg</td>
</tr>
</tbody>
</table>

*Acetadote is compatible with the following diluents; 5% Dextrose in Water, 0.45% Sodium Chloride Injection, and Sterile Water for Injection.

See also Section 2.2 Volume Adjustment: Patients less than 40 kg and Requiring Fluid Restriction

Dosing for patients who weigh 21 kg to 40 kg (Table 2):

- **Loading Dose**: 150 mg/kg diluted in 100 mL of diluent* administered over 1 hr
- **Second Dose**: 50 mg/kg diluted in 250 mL of diluent* administered over 4 hrs
- **Third Dose**: 100 mg/kg diluted in 500 mL of diluent* administered over 16 hrs

*Acetadote is compatible with the following diluents; 5% Dextrose in Water 0.45% Sodium Chloride Injection, and Sterile Water for Injection.

Table 2. Three Bag Method Dosage Guide by Weight in Patients 21 kg to 40 kg

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Bag 1 (loading dose): 150 mg/kg in 100 mL of diluent* infused over 1 hr</th>
<th>Bag 2 (second dose): 50 mg/kg in 250 mL of diluent* infused over 4 hrs</th>
<th>Bag 3 (third dose): 100 mg/kg in 500 mL of diluent* infused over 16 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acetadote Total Dose (mg)</td>
<td>Diluent volume (mL)</td>
<td>Acetadote Total Dose (mg)</td>
</tr>
<tr>
<td>21 kg</td>
<td>3,150 mg</td>
<td>1,050 mg</td>
<td>2,100 mg</td>
</tr>
<tr>
<td>30 kg</td>
<td>4,500 mg</td>
<td>1,500 mg</td>
<td>3,000 mg</td>
</tr>
<tr>
<td>40 kg</td>
<td>6,000 mg</td>
<td>2,000 mg</td>
<td>4,000 mg</td>
</tr>
</tbody>
</table>

Reference ID: 3319304
See also Section 2.2 Volume Adjustment: Patients less than 40 kg and Requiring Fluid Restriction.

Dosing for patients who weigh 41 kg to 100 kg (Table 3):

- **Loading Dose:** 150 mg/kg diluted in 200 mL of diluent* administered over 1 hr
- **Second Dose:** 50 mg/kg diluted in 500 mL of diluent* administered over 4 hrs
- **Third Dose:** 100 mg/kg diluted in 1000 mL of diluent administered over 16 hrs

| Table 3. Three Bag Method Dosage Guide by Weight in Patients 41 kg to 100 kg |
|-----------------|-----------------|-----------------|
| **Body Weight (kg)** | **Bag 1 (loading dose):** | **Bag 2 (second dose):** | **Bag 3 (third dose):** |
|                 | Acetadote Total Dose (mg) | Acetadote Total Dose (mg) | Acetadote Total Dose (mg) |
| 41 kg           | 6,150 mg            | 2,050 mg          | 4,100 mg             |
| 50 kg           | 7,500 mg            | 2,500 mg          | 5,000 mg             |
| 60 kg           | 9,000 mg            | 3,000 mg          | 6,000 mg             |
| 70 kg           | 10,500 mg           | 3,500 mg          | 7,000 mg             |
| 80 kg           | 12,000 mg           | 4,000 mg          | 8,000 mg             |
| 90 kg           | 13,500 mg           | 4,500 mg          | 9,000 mg             |
| 100 kg          | 15,000 mg           | 5,000 mg          | 10,000 mg            |

*Acetadote is compatible with the following diluents; 5% Dextrose 0.45% Sodium Chloride Injection, and Sterile Water for Injection.

Patients Weighing More Than 100 kg

No specific studies have been conducted to evaluate the use of or necessity of dosing adjustments in patients weighing over 100 kg. Limited information is available regarding the dosing requirements of patients that weigh more than 100 kg. The dose of Acetadote recommended in these patients should be a loading dose of 15,000 mg infused over a period of one hour followed by a first maintenance dose of 5,000 mg over 4 hours and a second maintenance dose of 10,000 mg over 16 hours (See Table 3).

Continued Therapy beyond 21 Hours

While there is no clinical trial data to support infusions beyond 21 hours there is literature that supports continued infusion of acetylcysteine in some rare instances. In cases of suspected massive overdose, or with concomitant ingestion of other substances, or in patients with preexisting liver disease, the absorption and/or the half-life of acetaminophen may be prolonged, in such cases consideration should be given to the need for continued infusion of N-acetylcysteine beyond 21 hours. Acetaminophen levels and ALT/AST & INR should be checked before the end of the 21-hour infusion. If acetaminophen levels are still detectable, or in cases in which the ALT/AST are still increasing or the INR remains elevated, the infusion should be continued, and the treating physician should contact a US regional poison center at 1-800-222-1222, or alternatively, a “special health professional assistance line for acetaminophen overdose” at 1-800-525-6115 for assistance with dosing recommendations.

2.2 Volume Adjustment: Patients less than 40 kg and Requiring Fluid Restriction

The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of diluent should be reduced as clinically needed. If the volume of the infusion is not adjusted, fluid overload can occur, potentially resulting in hyponatremia, seizure and death. [see Dosage and Administration (2)].

As Acetadote is hyperosmolar (2600 mOsmol/L), caution is advised when the diluent volume is decreased as the hyperosmolarity of the solution is increased. See Table 4 below for examples.

<table>
<thead>
<tr>
<th>Table 4. Acetadote Concentration and Osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetadote Concentration (mg/mL)</td>
</tr>
<tr>
<td>7 mg/mL</td>
</tr>
<tr>
<td>24 mg/m/L</td>
</tr>
</tbody>
</table>

*Osmolarity should be adjusted to a physiologically safe level, (generally not less than 150mOsmol/L in children).

Single dose vial, preservative-free, discard unused portion. If vial was previously opened, do not use for intravenous administration.

Stability studies indicate that the diluted solution is stable for 24 hours at controlled room temperature.

Note: The color of Acetadote may turn from essentially colorless to a slight pink or purple once the stopper is punctured. The color change does not affect the quality of the product.

2.3 Renal Impairment

No data are available to determine if a dose adjustment in patients with moderate or severe renal impairment is required.

2.4 Hepatic Impairment

Although there was a threefold increase in acetylcysteine plasma concentrations in patients with hepatic cirrhosis, no data are available to determine if a dose adjustment in these patients is required. The published medical literature does not indicate that the dose of acetylcysteine in patients with hepatic impairment should be reduced.

3 DOSAGE FORMS AND STRENGTHS

Each single dose vial contains 6g/30mL (200 mg/mL) of Acetadote (acetylcysteine) Injection. Acetadote is sterile and can be used for intravenous administration.

4 CONTRAINDICATIONS

Acetadote is contraindicated in patients with previous anaphylactoid reactions to acetylcysteine.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactoid Reactions
Serious anaphylactoid reactions, including death in a patient with asthma, have been reported in patients administered acetylcysteine intravenously.

Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 30 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. Anaphylactoid reactions (defined as the occurrence of an acute hypersensitivity reaction during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath), have been observed in patients receiving intravenous acetylcysteine for acetaminophen overdose and occurred soon after initiation of the infusion [see Adverse Reactions (6.1)]. If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as an anaphylactoid reaction. This usually entails administering antihistaminic drugs and in severe cases may require administration of epinephrine. In addition, the acetylcysteine infusion may be interrupted until treatment of the anaphylactoid symptoms has been initiated and then carefully restarted. If the anaphylactoid reaction returns upon reinitiation of treatment or increases in severity, intravenous acetylcysteine should be discontinued and alternative patient management should be considered.

5.2 Monitoring patients with asthma

Acetadote should be used with caution in patients with asthma, or where there is a history of bronchospasm.

5.3 Volume Adjustment: Patients less than 40 kg and Requiring Fluid Restriction

The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of diluent should be reduced as needed [see Dosage and Administration (2)]. If volume is not adjusted fluid overload can occur, potentially resulting in hyponatremia, seizure and death.

For specific treatment information regarding the clinical management of acetaminophen overdose, please contact your regional poison center at 1-800-222-1222, or alternatively, a special health professional assistance line for acetaminophen overdose at 1-800-525-6115.

6 ADVERSE REACTIONS

6.1 Clinical Studies 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.

In the literature the most frequently reported adverse reactions attributed to intravenous acetylcysteine administration were rash, urticaria and pruritus. The frequency of adverse reactions has been reported to be between 0.2% and 20.8%, and they most commonly occur during the initial loading dose of acetylcysteine.

Loading Dose/Infusion Rate Study

The incidence of drug-related adverse reactions occurring within the first 2 hours following intravenous acetylcysteine administration was 17% developed an anaphylactoid reaction (18% in the 15-minute treatment group; 14% in the 60-minute treatment group) in this randomized, open-label, multi-center clinical study conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the intravenous acetylcysteine loading dose [see Warnings (Section 5) and Clinical Studies - Loading Dose/Infusion Rate Study (Section 14)].

Table 5. Incidence of Drug-Related Adverse Reactions Occurring Within the First 2 Hours Following Study Drug Administration by Preferred Term: Loading Dose/Infusion Rate Study

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>15-mins</th>
<th>60-mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>n=109</td>
<td>n=71</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>16 (15%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>16 (15%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>20 (18%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>2 (2%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Postmarketing Safety Study

A large multi-center study was performed in Canada where data were collected from patients who were treated with intravenous acetylcysteine for acetaminophen overdose between 1980 and 2005. This study evaluated 4709 adult cases and 1905 pediatric cases. The incidence of anaphylactoid reactions in adult (overall incidence 7.9%) and pediatric (overall incidence 9.5%) patients is presented in Tables 6 and 7.

Table 6. Distribution of reported reactions in adult patients receiving intravenous acetylcysteine

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria/Facial Flushing</td>
<td>6.1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4.3%</td>
</tr>
<tr>
<td>Respiratory Symptoms*</td>
<td>1.9%</td>
</tr>
<tr>
<td>Edema</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Table 7. Distribution of reported reactions in pediatric patients receiving intravenous acetylcysteine

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria/Facial flushing</td>
<td>7.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4.1%</td>
</tr>
<tr>
<td>Respiratory Symptoms*</td>
<td>2.2%</td>
</tr>
<tr>
<td>Edema</td>
<td>1.2%</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Respiratory symptoms are defined as presence of any of the following: cough, wheezing, stridor, shortness of breath, chest tightness, respiratory distress, or bronchospasm.

7 DRUG INTERACTIONS
No drug-drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B

There are no adequate and well-controlled studies of Acetadote in pregnant women. However, limited case reports of pregnant women exposed to acetylcysteine during various trimesters did not report any adverse maternal, fetal or neonatal outcomes.

There are published reports on four pregnant women with acetaminophen toxicity, who were treated with oral or intravenous acetylcysteine at the time of delivery. Acetylcysteine crossed the placenta and was measurable following delivery in serum and cord blood of three viable infants and in cardiac blood of a fourth infant at autopsy (22 weeks gestational age who died 3 hours after birth). No adverse sequelae developed in the three viable infants. All mothers recovered and none of the infants had evidence of acetaminophen poisoning.

Reproduction studies were performed in rats at oral doses up to 2000 mg/kg/day (1.1 times the recommended total human intravenous dose of 300 mg/kg based on body surface area comparison) and in rabbits at oral doses up to 1000 mg/kg/day (1.1 times the recommended total human intravenous dose of 300 mg/kg based on body surface area comparison). No effects on fertility or harm to the fetus due to acetylcysteine were observed.

8.3 Nursing mothers
It is not known whether Acetadote is present in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetylcysteine is administered to a nursing woman. Based on the pharmacokinetics of acetylcysteine, it should be nearly completely cleared 30 hours after administration. Nursing women may consider resuming nursing 30 hours after administration.

8.4 Pediatric use
No adverse effects were noted during intravenous infusion with acetylcysteine at a mean rate of 4.2 mg/kg/h for 24 hours to 10 preterm newborns ranging in gestational age from 25 to 31 weeks and in weight from 500 to 1380 grams in one study or in 6 newborns ranging in gestational age from 26 to 30 weeks and in weight from 520 to 1335 grams infused with acetylcysteine at 0.1 to 1.3 mg/kg/h for 6 days. Elimination of acetylcysteine was slower in these infants than in adults; mean elimination half-life was 11 hours. There are no adequate and well-controlled studies in pediatric patients.

8.5 Geriatric use
The clinical studies do not provide a sufficient number of geriatric subjects to determine whether the elderly respond differently.

10 OVERDOSAGE
Single intravenous doses of acetylcysteine at 1000 mg/kg in mice, 2445 mg/kg in rats, 1500 mg/kg in guinea pigs, 1200 mg/kg in rabbits and 500 mg/kg in dogs were lethal. Symptoms of acute toxicity were ataxia, hypoactivity, labored respiration, cyanosis, loss of righting reflex and convulsions.

11 DESCRIPTION
Acetylcysteine injection is an intravenous antidote for the treatment of acetaminophen overdose. Acetylcysteine is the nonproprietary name for the N-acetyl derivative of the naturally occurring amino acid, L-cysteine (N-acetyl-L-cysteine,). The compound is a white crystalline powder, which melts in the range of 104° to 110°C and has a very slight odor. The molecular formula of the compound is C₇H₁₄N₂O₃S, and its molecular weight is 163.2. Acetylcysteine has the following structural formula:

Acetadote is supplied as a sterile solution in vials containing 20% w/v (200 mg/mL) acetylcysteine. The pH of the solution ranges from 6.0 to 7.5. Acetadote contains the following inactive ingredients: sodium hydroxide (used for pH adjustment), and Sterile Water for Injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of action
Acetaminophen Overdose:
Acetaminophen is absorbed from the upper gastrointestinal tract with peak plasma levels occurring between 30 and 60 minutes after therapeutic doses and usually within 4 hours following an overdose. It is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are excreted in the urine. A small fraction of an ingested dose is metabolized in the liver by isozyme CYP2E1 of the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite. The toxic metabolite preferentially conjugates with hepatic glutathione to form nontoxic cysteine and mercapturic acid derivatives, which are then excreted by the kidney. Recommended therapeutic doses of acetaminophen are not believed to saturate the glucuronide and sulfate conjugation pathways and therefore are not expected to result in the formation of sufficient reactive
metabolite to deplete glutathione stores. However, following ingestion of a large overdose, the glucuronide and sulfate conjugation pathways are saturated resulting in a larger fraction of the drug being metabolized via the cytochrome P-450 pathway and therefore, the amount of acetaminophen metabolized to the reactive intermediate increases. The increased formation of the reactive metabolite may deplete the hepatic stores of glutathione with subsequent binding of the metabolite to protein molecules within the hepatocyte resulting in cellular necrosis.

**Acetylcysteine Intravenous Treatment:**

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. It is most effective when given early, with benefit seen principally in patients treated within 8-10 hours of the overdose. Acetylcysteine likely protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

**12.3 Pharmacokinetics**

**Distribution:**

The steady-state volume of distribution (Vdss) and the protein binding for acetylcysteine were reported to be 0.47 liter/kg and 83%, respectively.

**Metabolism:**

Acetylcysteine may form cysteine, disulfides and conjugates in vivo (N, N'-diacetylcyesteine, N-acetylcysteine-cysteine, N-acetylcysteine-glutathione, N-acetylcysteine-protein, etc). Based on published data, it was reported that after an oral dose of $^{35}$S-acetylcysteine, about 22% of total radioactivity was excreted in urine after 24 hours. No metabolites were identified.

**Elimination:**

After a single intravenous dose of acetylcysteine, the plasma concentration of total acetylcysteine declined in a poly-exponential decay manner with a mean terminal half-life (T1/2) of 5.6 hours. The mean clearance (CL) for acetylcysteine was reported to be 0.11 liter/hr/kg and renal CL constituted about 30% of total CL.

**Special Populations:**

**Gender:** Adequate information is not available to assess if there are differences in pharmacokinetics (PK) between males and females.

**Pediatric:**

The mean elimination T1/2 of acetylcysteine is longer in newborns (11 hours) than in adults (5.6 hours). Pharmacokinetic information is not available in other age groups.

**Pregnant Women:** In four pregnant women with acetaminophen toxicity, oral or intravenous acetylcysteine was administered at the time of delivery. Acetylcysteine was detected in the cord blood of 3 viable infants and in cardiac blood of a fourth infant sampled at autopsy [see Pregnancy (8.1)].

**Hepatic Impairment:** In subjects with severe liver damage, i.e., cirrhosis due to alcohol (with Child-Pugh score of 7-13), or primary and/or secondary biliary cirrhosis (with Child-Pugh score of 5-7), mean T1/2 increased by 80% while mean CL decreased by 30% compared to the control group.

**Renal Impairment:** Pharmacokinetic information is not available in patients with renal impairment.

**Geriatric Patients:** Adequate information on acetylcysteine PK in geriatric patients is not available.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of acetylcysteine.

Acetylcysteine was not genotoxic in the Ames test or the in vivo mouse micronucleus test. It was, however, positive in the in vitro mouse lymphoma cell (L5178Y/Tk+/-) forward mutation test.

Treatment of male rats with acetylcysteine at an oral dose of 250 mg/kg/day for 15 weeks (0.1 times the recommended total human intravenous dose of 300 mg/kg based on body surface comparison) did not affect the fertility or general reproductive performance.

**14 CLINICAL STUDIES**

**Loading Dose/Infusion Rate Study**

A randomized, open-label, multi-center clinical study was conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the intravenous acetylcysteine loading dose. One hundred nine subjects were randomized to a 15 minute infusion rate and seventy-one subjects were randomized to a 60 minute infusion rate. The loading dose was 150 mg/kg followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. Of the 180 patients, 27% were male and 73% were female. Ages ranged from 15 to 83 years, with the mean age being 29.9 years (±13.0).

A subgroup of 58 subjects (33 in the 15-minute treatment group; 25 in the 60-minute treatment group) was treated within 8 hours of acetaminophen ingestion. No hepatotoxicity occurred within this subgroup; however with 95% confidence, the true hepatotoxicity rates could range from 0% to 9% for the 15-minute treatment group and from 0% to 12% for the 60-minute treatment group.

**Observational Study**

An open-label, observational database contained information on 1749 patients who sought treatment for acetaminophen overdose over a 16-year period. Of the 1749 patients, 65% were female, 34% were male and less than 1% was transgender. Ages ranged from 2 months to 96 years, with 71.4% of the patients falling in the 16-40 year old age bracket. A total of 399 patients received acetylcysteine treatment. A post-hoc analysis identified 56 patients who (1) were at high or probable risk for hepatotoxicity (APAP greater than 150 mg/L at the four hours line according to the Australian nomogram) and (2) had a liver function test. Of the 53 patients who were treated with intravenous acetylcysteine (300 mg/kg intravenous acetylcysteine administered over 20-21 hours) within 8 hours, two (4%) developed hepatotoxicity (AST or ALT greater than 1000 U/L). Twenty-one of 48 (44%) patients treated with acetylcysteine after 15 hours developed hepatotoxicity. The actual number of hepatotoxicity outcomes may be higher than what is reported here. For patients with multiple admissions for acetaminophen overdose, only the first overdose treated with intravenous acetylcysteine was examined. Hepatotoxicity may have occurred in subsequent admissions.
Evaluable data were available from a total of 148 pediatric patients (less than 16 years of age) who were admitted for poisoning following ingestion of acetaminophen, of whom 23 were treated with intravenous acetylcysteine. Of the 23 patients who received intravenous acetylcysteine treatment, 3 patients (13%) had an adverse reaction (anaphylactoid reaction, rash and flushing, transient erythema). There were no deaths of pediatric patients. None of the pediatric patients receiving intravenous acetylcysteine developed hepatotoxicity while two patients not receiving intravenous acetylcysteine developed hepatotoxicity. The number of pediatric patients is too small to provide a statistically significant finding of efficacy; however the results appear to be consistent to those observed for adults.

Postmarketing Safety Study [see 6.1 Clinical Studies Experience]

16 HOW SUPPLIED/STORAGE AND HANDLING
Acetadote (acetylcysteine) Injection is available as a 20% solution (200mg/mL) in 30 mL single dose glass vials. Each single dose vial contains 6g/30mL (200 mg/mL) of Acetadote Injection. Acetadote is sterile and can be used for intravenous administration. It is available as follows:
- 30 mL vials, carton of 4 (NDC 66220-207-30)

Do not use previously opened vials for intravenous administration.

Note: The color of Acetadote may turn from essentially colorless to a slight pink or purple once the stopper is punctured. The color change does not affect the quality of the product.

The stopper in the Acetadote vial is formulated with a synthetic base-polymer and does not contain Natural Rubber Latex, Dry Natural Rubber, or blends of Natural Rubber.

Storage
Store unopened vials at controlled room temperature, 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
Sensitivity to acetylcysteine: Patients should be advised to report to their physician any history of sensitivity to acetylcysteine [see Contraindications (4)].

Asthma: Patients should be advised to report to their physician any history of asthma [see Warnings and Precautions (5)].

For all questions concerning adverse reactions associated with the use of this product or for inquiries concerning our products, please contact us at 1-877-484-2700. For specific treatment information regarding the clinical management of acetaminophen overdose, please contact your regional poison center at 1-800-222-1222, or alternatively, a special health professional assistance line for acetaminophen overdose at 1-800-525-6115.

Manufactured for:
Cumberland Pharmaceuticals Inc.
Nashville, TN 37203

*Sections or subsections omitted from the Full Prescribing Information are not listed.