HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACETYLCYSTEINE INJECTION safely and effectively. See full prescribing information for ACETYLCYSTEINE INJECTION.
ACETYLCYSTEINE INJECTION
Initial U.S. Approval: 2004.

RECENT MAJOR CHANGES

Adverse Reactions, Postmarketing Safety Study (6.1) 12/2008

INDICATIONS AND USAGE

Acetylcysteine Injection, administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, is indicated to prevent or lessen hepatic injury (1)

DOSAGE AND ADMINISTRATION

Patients ≥40 kg (2.1):
Loading Dose: 150 mg/kg in 200 mL of diluent administered over 60 min
Dose 2: 50 mg/kg in 500 mL of diluent administered over 4 hr
Dose 3: 100 mg/kg in 1000 mL of diluent administered over 16 hr

Patients >20- <40 kg (2.1):
Loading Dose: 150 mg/kg in 100 mL of diluent administered over 60 min
Dose 2: 50 mg/kg in 250 mL of diluent administered over 4 hr
Dose 3: 100 mg/kg in 500 mL of diluent administered over 16 hr

Patients ≤20 kg (2.1):
Loading Dose: 150 mg/kg in 3 mL/kg of body weight of diluent administered over 60 min
Dose 2: 50 mg/kg in 7 mL/kg of body weight of diluent administered over 4 hr
Dose 3: 100 mg/kg in 14 mL/kg of body weight of diluent administered over 16 hr

DOSAGE FORMS AND STRENGTHS

Vials: 200 mg/mL, 30 mL (20% solution) (3)

CONTRAINDICATIONS

Patients with previous anaphylactoid reaction to acetylcysteine (4)

WARNINGS AND PRECAUTIONS

- Monitor as acute flushing and erythema of the skin may occur; usually associated with the loading dose; often resolves spontaneously despite continued infusion (5.1)
- Monitor for serious anaphylactoid reactions; infusion may be interrupted until treatment of anaphylactoid symptoms has been initiated (5.1)
- Should be used with caution in patients with asthma, or where there is a history of bronchospasm (5.2)
- Total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2%) are rash, urticaria/facial flushing and pruritus (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact APP Pharmaceuticals, LLC, Medical Affairs at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at 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 < 40 kg (2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

Acetylcysteine Injection, administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, is indicated to prevent or lessen hepatic injury [see **DOSAGE AND ADMINISTRATION (2)** and **Acetaminophen Assays – Interpretation and Methodology (1.1, 1.2)**].

On admission for suspected 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.

Acetylcysteine Injection 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, Acetylcysteine Injection 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 aminotranferase (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

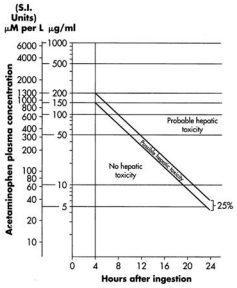
1. When results of the plasma acetaminophen assay are available, refer to the nomogram in Figure 1 to determine if plasma concentration is in the potentially toxic range. Values above the line connecting 200 mcg/mL at 4 hours with 50 mcg/mL at 12 hours (probable line) are associated with a probability of hepatic toxicity if an antidote is not administered.

2. If the predetoxification 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 predetoxification 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.

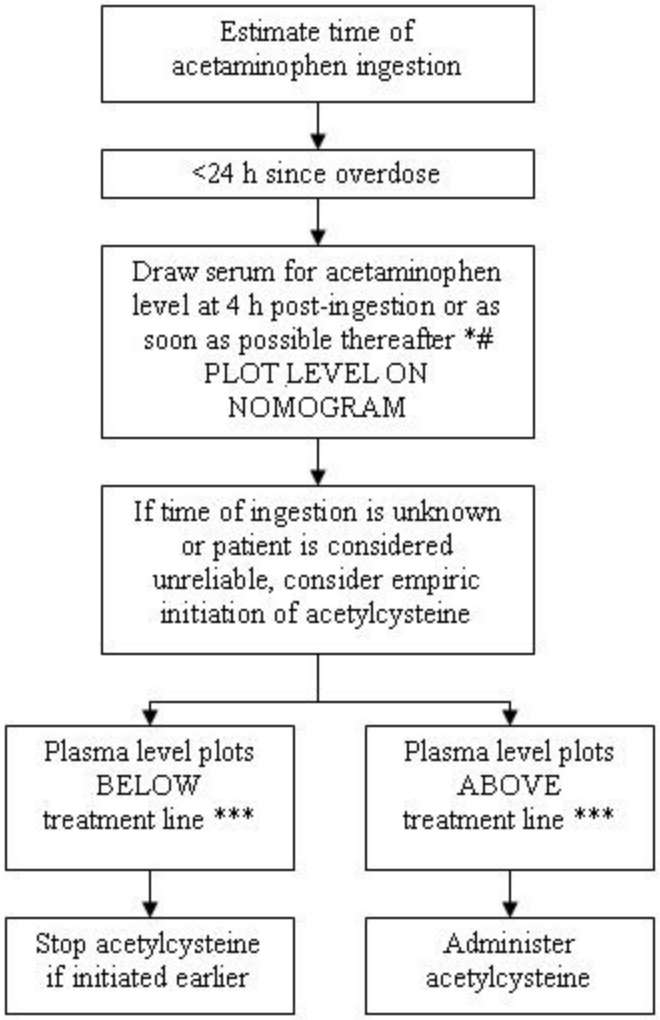
Figure 1. Rumack-Matthew Nomogram: Plasma or Serum Acetaminophen Concentration vs. Time Post Acetaminophen Ingestion (Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics. 1975;55:871-876 and Rumack BH, Peterson RC, Kock GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med. 1981;141:380-385).



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. Acetylcysteine Injection Treatment Flow Chart



*Acetaminophen levels drawn less than 4 hours post-ingestion may be misleading.
With 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.
***Acetylcysteine 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 & ADMINISTRATION

The total dose of Acetylcysteine Injection is 300 mg/kg administered over 21 hours.Please refer to the guidelines below for dose preparation based upon patient weight.

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

Patients ≥ 40 kg (Table 1):

Loading Dose: 150 mg/kg in 200 mL of diluent* administered over 60 min
Second Dose: 50 mg/kg in 500 mL of diluent administered over 4 hr
Third Dose: 100 mg/kg in 1000 mL of diluent administered over 16 hr

Table 1. Three-Bag Method Dosage Guide by Weight, patients ≥ 40 kg

Body Weight	LOADING Dose 150 mg/kg in 200 mL diluent * over 60 min	SECOND Dose 50 mg/kg in 500 mL diluent over 4 hours	THIRD Dose 100 mg/kg in 1000 mL diluent over 16 hours

(kg)	(lb)	Acetylcysteine Injection (mL)	Acetylcysteine Injection (mL)	Acetylcysteine Injection (mL)
100	220	75	25	50
90	198	67.5	22.5	45
80	176	60	20	40
70	154	52.5	17.5	35
60	132	45	15	30
50	110	37.5	12.5	25
40	88	30	10	20

*Acetylcysteine Injection is hyperosmolar (2600 mOsm/L) and is compatible with 5% Dextrose (D5W), ½Normal Saline (0.45% Sodium Chloride Injection, ½ NS), and Water for Injection (WFI).
The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction:

Patients >20 - <40 kg (Table 2):
Loading Dose: 150 mg/kg in 100 mL of diluent* administered over 60 min
Second Dose: 50 mg/kg in 250 mL of diluent administered over 4 hr
Third Dose: 100 mg/kg in 500 mL of diluent administered over 16 hr

Table 2. Three-Bag Method Dosage Guide by Weight, patients >20 - < 40 kg

Body Weight		LOADING Dose 150 mg/kg over 60 minutes		SECOND Dose 50 mg/kg over 4 hours	THIRD Dose 100 mg/kg over 16 hours
(kg)	(lb)	Acetylcysteine Injection(mL)	Diluent* (mL)	Acetylcysteine Injection (mL)	Acetylcysteine Injection (mL)
30	66	22.5	100	75	150
25	55	18.75	100	62.5	125

*Acetylcysteine Injection is hyperosmolar (2600 mOsm/L) and is compatible with 5% Dextrose (D5W), ½Normal Saline (0.45% Sodium Chloride Injection, ½ NS), and Water for Injection (WFI).

Patients ≤20 kg (Table 3):
Loading Dose: 150 mg/kg in 3 mL/kg of body weight of diluent* administered over 60 min
Second Dose: 50 mg/kg in 7 mL/kg of body weight of diluent administered over 4 hr
Third Dose: 100 mg/kg in 14 mL/kg of body weight of diluent administered over 16 hr

Table 3. Three-Bag Method Dosage Guide by Weight, patients ≤ 20 kg

Body Weight		LOADING Dose 150 mg/kg over 60 minutes		SECOND Dose 50 mg/kg over 4 hours		THIRD Dose 100 mg/kg over 16 hours	
(kg)	(lb)	Acetylcysteine Injection (mL)	Diluent*(mL)	Acetylcysteine Injection(mL)	Diluent (mL)	Acetylcysteine Injection(mL)	Diluent (mL)

20	44	15	60	5	140	10	280
15	33	11.25	45	3.75	105	7.5	210
10	22	7.5	30	2.5	70	5	140

*Acetylcysteine Injection is hyperosmolar (2600 mOsm/L) and is compatible with 5% Dextrose (D5W), ½Normal Saline (0.45% Sodium Chloride Injection, ½ NS), and Water for Injection (WFI).
Single dose vial, preservative-free, discard unused portion. If vial was previously opened, do not use for I.V. administration. Stability studies indicate that the diluted solution is stable for 24 hours at controlled room temperature.
Note: The color of Acetylcysteine Injection may turn from essentially colorless to a slight pink color once the stopper is punctured. The color change does not affect the quality of the product.

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

2.3 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 & STRENGTHS
Acetylcysteine Injection is available as a 20% solution (200 mg/mL) in 30 mL single dose glass vials. Acetylcysteine Injection is sterile and can be used for I.V. administration.

4 CONTRAINDICATIONS
Acetylcysteine Injection 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 I.V. 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
Acetylcysteine Injection should be used with caution in patients with asthma, or where there is a history of bronchospasm.

5.3 Volume Adjustment: Patients <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 I.V. 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 acetylcysteine administration reported in a randomized study in patients with acetaminophen poisoning is presented in Table 4 by preferred term. In this study patients were randomized to a 15-minute or a 60-minute loading dose regimen.

Within the first 2 hours following I.V. acetylcysteine administration, 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 I.V. acetylcysteine loading dose [see **WARNINGS (Section 5)** and CLINACAL STUDIES - Loading Dose/InfusionRate Study(Section 14**)**].

Table 4. Incidence of Drug-Related Adverse Reactions Occurring Within the First 2 Hours Following Study Drug Administration by Preferred Term: Loading Dose/Infusion Rate Study

Treatment Group	**15-min**				**60-min**			
Number of Patients	**n=109**				**n=71**			
Cardiac disorders	5 (5%)				2 (3%)			
	Unkn	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Severity:								
Tachycardia NOS		4 (4%)	1 (1%)			2 (3%)		
Gastrointestinal disorders	16 (15%)				7 (10%)			
	Unkn	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Severity:								
Nausea	1(1%)		6 (6%)			1 (1%)	1 (1%)	
Vomiting NOS		2 (2%)	11 (10%)			2 (3%)	4 (6%)	
Immune System Disorders	20 (18%)				10 (14%)			
	Unkn	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Severity:								
Anaphylactoid reaction	2(2%)	6 (6%)	11 (10%)	1 (1%)		4 (6%)	5 (7%)	1 (1%)
Respiratory, thoracic and	2 (2%)				2 (3%)			

mediastinal disorders								
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Pharyngitis			1 (1%)					
Rhinorrhoea		1 (1%)						
Rhonchi						1 (1%)		
Throat tightness						1 (1%)		
Skin & subcutaneous tissue disorders	6 (6%)				5 (7%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Pruritus		1 (1%)				2 (3%)		
Rash NOS		3 (3%)	2 (2%)			3 (4%)		
Vascular disorders	2 (2%)				3 (4%)			
Severity:	*Unkn*	*Mild*	*Moderate*	*Severe*	*Unkn*	*Mild*	*Moderate*	*Severe*
Flushing		1 (1%)	1 (1%)			2 (3%)	1 (1%)	

Unkn=Unknown

Postmarketing Safety Study

A large multi-center study was performed in Canada where data were collected from patients who were treated with I.V. NAC 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 5 and 6.**

Table 5.Distribution of reported reactions in adult patients receiving I.V. NAC

	Incidence (%)
Reaction	**% of Patients (n=4709)**
Urticaria/Facial Flushing	6.1%
Pruritus	4.3%

Respiratory Symptoms*	1.9%
Edema	1.6%
Hypotension	0.1%
Anaphylaxis	0.1%

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

Table 6. **Distribution of reported reactions in pediatric patients receiving I.V. NAC**

	Incidence (%)
Reaction	**% of Patients (n=1905)**
Urticaria/Facial Flushing	7.6%
Pruritus	4.1%
Respiratory Symptoms*	2.2%
Edema	1.2%
Anaphylaxis	0.2%
Hypotension	0.1%

*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 Acetylcysteine Injection 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.

Reproductive and developmental toxicity studies performed in rats at oral doses up to 6.7 times the recommended human intravenous dose and in rabbits at doses up to 3.3 times the recommended human intravenous dose revealed no evidence of impaired fertility or embryofetal toxicity [see Reproductive and Developmental Toxicology (13.3)**].**

8.3 Nursing Mothers

It is not known whether Acetylcysteine Injection 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

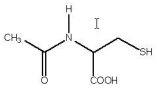
No adverse effects were noted during I.V. infusion with acetylcysteine at a mean rate of 4.2 mg/kg/h for 24 hours to 10 preterm newborns ranging in gestational age from 25 to 31 weeks and in weight from 500 to 1380 grams in one study or in 6 newborns ranging in gestational age from 26 to 30 weeks and 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 (I.V.) medication 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, NAC). 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 $C_5H_9NO_3S$, and its molecular weight is 163.2. Acetylcysteine has the following structural formula:



Acetylcysteine Injection 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. AcetylcysteineInjection contains the following inactive ingredients: 0.5 mg/mL disodium edetate, sodium hydroxide (used for pH adjustment), and 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 glucoronide 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 I.V. 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 (Vd_{ss}) 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'-diacetylcysteine, 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 ($T_{1/2}$) 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 $T_{1/2}$ 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 I.V. 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 $T_{1/2}$ 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 & Mutageneis & 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 (0.8 times the recommended human dose of 300 mg/kg) did not affect the fertility or general reproductive performance.

13.3 Reproductive and Developmental Toxicology
Reproduction studies were performed in rats at oral doses up to 2000 mg/kg/day (6.7 times the recommended human dose of 300 mg/kg) and in rabbits at oral doses up to 1000 mg/kg/day (3.3 times the recommended human dose of 300 mg/kg) and revealed no evidence of impaired fertility or harm to the fetus due to acetylcysteine [see **Pregnancy (8.1)**].

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 I.V. 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 <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 >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 I.V. acetylcysteine (300 mg/kg I.V. acetylcysteine administered over 20-21 hours) within 8 hours, two (4%) developed hepatotoxicity (AST or ALT>1000U/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 I.V. 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 I.V. acetylcysteine. Of the 23 patients who received I.V. 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 I.V. acetylcysteine developed hepatotoxicity while two patients not receiving I.V. 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
Acetylcysteine Injection is available as a **20% solution (200 mg/mL)** in 30 mL single dose glass vials. Acetylcysteine Injection is sterile and can be used for I.V. administration.

Acetylcysteine injection is available as:

Product No.	NDC No	Strength	
963030	63323-963-30	200 mg/ml	20% solution (200 mg/ml)in 30 mL single dose glass vials, packaged in cartons of 4.

Do not use previously opened vials for I.V. administration.

Note: The color of Acetylcysteine Injection 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 Acetylcysteine Injection 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 1-800-551-7176.

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:

APP

APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in India
451234/Issued: May 2011

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

18 PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 63323-963-30 963030

Acetylcysteine Injection

6 g per 30 mL

(200 mg/mL)

FOR INTRAVENOUS USE

Discard unused portion

30 mL sterile Vial Rx only

76 x 76 x 72 mm

CAR-008539-01

NDC 63323-963-30 963030

ACETYLCYSTEINE
INJECTION

6 g per 30 mL

(200 mg/mL)

FOR INTRAVENOUS USE
Discard unused portion

4 x 30 mL Sterile Vials

APP

Store at 20°C - 25°C (68°F - 77°F) [See USP controlled room temperature].

Each mL contains 200 mg Acetylcysteine, 0.5 mg disodium edetate USP, Sodium Hydroxide NF (used for pH adjustment) and Water for Injection USP.

Single dose vial, preservative free.
Latex Free
Do not use if previously opened.
Usual Dosage: See package insert for dosage information.
Manufactured for:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
M.L. : 103/AP/RR/97/F/R
Made in India

621174

(01) 20363323963303

Lot:

EXP:

Unvarnish Area
35 x 17.5 mm

NDC 63323-963-30 963030

ACETYLCYSTEINE
INJECTION

6 g per 30 mL

(200 mg/mL)

FOR INTRAVENOUS USE
Discard unused portion

4 x 30 mL Sterile Vials

APP

NDC 63323-963-30 963030

ACETYLCYSTEINE
INJECTION

6 g per 30 mL

(200 mg/mL)

FOR INTRAVENOUS USE
Discard unused portion

4 x 30 mL Sterile Vials

APP

Rx only