℞ Acetylcysteine Injection BP 20%

NACVENT™-1000

FOR I.V. USE ONLY

1. Generic Name :
Acetylcysteine Injection BP 20%
2. Qualitative and Quantitative Composition :
Each vial contains:
Acetylcysteine IP 200 mg
Water for Injections IP q.s.
3. Pharmaceutical form :
Infusion concentrate
4. Clinical Particulars :
4.1 Therapeutic indications :
N-acetylcysteine is indicated for the treatment of paracetamol overdose in patients:
- who present within 15 hours after an acute overdose with a plasma paracetamol level on or above a line joining points of 150mg/L at 4h and 20mg/L at 15h (see nomogram below) or
- who have taken more than 200mg/kg or 12g (whichever is less) of ingested release paracetamol or two or more of two serum paracetamol levels taken four hours apart on or above a line joining points of 150mg/L at 4h and 20mg/L at 15h (see nomogram below) or
- Will or have taken an acute overdose of paracetamol with opiates or medicines with anticholinergic effects and have one of two serum paracetamol levels taken four hours apart on or above a line joining points of 100mg/L at 4h and 20mg/L at 15h (see nomogram below) or
- where there is any doubt over the time of an acute overdose, irrespective of plasma paracetamol level or
- who present more than 15 hours after an overdose with abnormal liver biochemistry (INR > 1.3 and/or > 10 fold normal hepatic ALT) or
- who have taken a staggered overdose irrespective of plasma paracetamol level. Staggered is defined as an overdose of 200mg/kg or 12g (whichever is less) over a single 24 hour period or 150mg/kg/day (whichever is less) per 24 hour period for at least 48 hours.

Plasma Paracetamol nomogram

Dose and method of administration
Acetylcysteine should be administered by intravenous infusion preferably using glucose 5% as the infusion fluid. Sodium chloride 0.9% solution may be used if glucose 5% is not suitable. The majority of patients should be treated with the three infusion schedule. However some patients may require prolonged treatment. Patients who have been very large overdoses (eg. 50g of paracetamol), co-ingested opiates or medicines with anticholinergic effects, or have taken modified release paracetamol should be assessed at the end of the normal dose schedule. Treatment should be continued until laboratory assessment shows liver enzymes improving, INR is 1.3 or less and there is no acidosis.

Dose in Adults
Acetylcysteine 200mg/ml, Injection is infused in three intravenous infusions containing different doses. This will give a total dose of 300 milligrams/kg of acetylcysteine infused over 21 hours.
INITIAL INFUSION: An initial dose of 100 milligrams/kg of acetylcysteine diluted in 200 mL of 5% glucose and infused over 60 minutes. SECOND INFUSION: 50 milligrams/kg of acetylcysteine in 500 mL of 5% glucose over the next 4 hours.
THIRD INFUSION: 100 milligrams/kg of acetylcysteine in 1000 mL of 5% glucose over the next 16 hours. The dose **should be calculated using the patient's actual weight** to a ceiling of 110kg for obese patients.

Regimen	Dose 1			Dose 2			Dose 3		
Fluid	200mL 5% glucose or sodium chloride 0.9%			500mL 5% glucose or sodium chloride 0.9%			1000mL 5% glucose or sodium chloride 0.9%		
Duration of Infusion	60 minutes			4 hours			16 hours		
Medicine Dose	150mg/kg N-acetylcysteine			50mg/kg N-acetylcysteine			100mg/kg N-acetylcysteine		
Patient weight kg	Dose mg	Ampoule volume* mL	Infusion rate mL/h	Dose mg	Ampoule volume* mL	Infusion rate mL/h	Dose mg	Ampoule volume* mL	Infusion rate mL/h
40-49	6750	34	204	2250	12	128	4500	23	64
50-59	8250	42	242	2750	14	129	5500	28	64
60-69	9750	49	249	3250	17	129	6500	33	65
70-79	11250	57	257	3750	19	130	7500	38	65
80-89	12750	64	264	4250	22	131	8500	43	65
90-99	14250	72	272	4750	24	131	9500	48	66
100-109	15750	79	279	5250	27	132	10500	53	66
>110	16500	83	283	5500	28	132	11000	55	66

*Dose calculations are based on the weight in the middle of the band
*Ampoule volume has been rounded up to the nearest whole number

Dose in Children Children should be treated with the same dosage and regimen as adults; however the quantity of intravenous fluid used must be modified to take into account age and weight as fluid overload is a potential danger. The full course of treatment with acetylcysteine includes three consecutive intravenous infusions. INITIAL INFUSION: An initial dose of 100 milligrams/kg of acetylcysteine given as a 50mg/mL solution at a rate of 3mL/kg/h. SECOND INFUSION: 50 milligrams/kg of acetylcysteine over the next 4 hours. Given as a 25.2mg/mL solution at a rate of 3mL/kg/h THIRD INFUSION: 100 milligrams/kg of acetylcysteine over the next 16 hours. Given as a 6.25mg/mL solution at a rate of 1mL/kg/h. Time **should be calculated using the patient's actual weight**. Determine the total volume of solution needed from the table.

Preparation of the solution
Initial infusion: To prepare a 50mg/mL solution, dilute each 10mL ampoule of acetylcysteine (200mg/mL) with 30mL glucose 5% or sodium chloride 0.9% to a total volume of 40mL. Second infusion: To prepare a 6.25mg/mL solution, dilute each 10mL ampoule of acetylcysteine (200mg/mL) with 31mL glucose 5% or sodium chloride 0.9% to give a total volume of 320mL. Third infusion: To prepare a 6.25mg/mL solution, dilute each 10mL ampoule of acetylcysteine (200mg/mL) with 31mL glucose 5% or sodium chloride 0.9% to give a total volume of 320mL.
Third infusion: To prepare a 6.25mg/mL solution, dilute each 10mL ampoule of acetylcysteine (200mg/mL) with 31mL glucose 5% or sodium chloride 0.9% to give a total volume of 320mL.

Regimen	Dose 1			Dose 2			Dose 3		
Medicine dose	150mg/kg (Neocysteine)			50mg/kg (Neocysteine)			100mg/kg (Neocysteine)		
Duration of infusion	1 hour			4 hours			16 hours		
Infusion rate	3mL/kg/h			3mL/kg/h			1mL/kg/h		
Patient weight	Dose	Ampoule volume*	Total infusion volume	Dose	Ampoule volume*	Total infusion volume	Dose	Ampoule volume*	Total infusion volume
40	6000	30	240 ml	2000	10	160 ml	4000	20	160 ml
45	6750	34	270 ml	2250	12	180 ml	4500	23	180 ml
50	7500	38	300 ml	2500	13	200 ml	5000	25	200 ml
55	8250	42	330 ml	2750	14	220 ml	5500	28	220 ml
60	9000	45	360 ml	3000	15	240 ml	6000	30	240 ml
65	9750	49	390 ml	3250	17	260 ml	6500	33	260 ml
70	10500	53	420 ml	3500	18	280 ml	7000	35	280 ml
75	11250	57	450 ml	3750	19	300 ml	7500	38	300 ml
80	12000	60	480 ml	4000	20	320 ml	8000	40	320 ml
85	12750	64	510 ml	4250	22	340 ml	8500	43	340 ml
90	13500	68	540 ml	4500	23	360 ml	9000	45	360 ml
95	14250	72	570 ml	4750	24	380 ml	9500	48	380 ml
100	15000	75	600 ml	5000	25	400 ml	10000	50	400 ml
>110	16500	83	660 ml	5500	28	440 ml	11000	55	440 ml

For example for a child weighing 12kg, 36ml, of solution is required for dose infusion 1 : 108ml, for dose infusion 2 : ml 240 ml, for dose infusion 3 : 0 ml 1 to infusion at 36ml/h over 60 mins, dose 2 is infused at 36ml/h and dose 3 at 12ml/h. Acetylcysteine is not compatible with rubber and some metals, particularly, iron, copper and nickel. Acetylcysteine 200mg/ml, Injection can be sued satisfactorily with silicone rubber and plastic.

Contraindications
There are no contraindications to the treatment of paracetamol overdose with acetylcysteine.

Special warnings and precautions for use
Management of Paracetamol Overdose
It should be noted that, after an ingestion of a potentially fatal dose of paracetamol, the patient may appear relatively well initially and may even continue normal activities for a day or two before the onset of hepatic failure. Hepatic damage is more likely to occur with a lower dosage of paracetamol in patients who have a history of liver disease, chronic alcoholism, or who are receiving drug ingestion (e.g. isoniazid, rifampicin, anticonvulsants including carbamazepine, phenobarbitone, primidone, sodium valproate). Patients may be unreliable as to the amount of drug ingested and the time of ingestion. Hepatic necrosis is preventable if treatment can be initiated within 15 to 12 hours of ingestion.
Hepatic necrosis has been seen with 8 grams of paracetamol, and death with 15 grams. Patient Presenting Within 15 Hours of Ingestion
Give activated charcoal (1 – 2 grams/kg) if it is within 1 hour of paracetamol ingestion, and the patient's conscious state is not impaired. In the event of overdose with sustained release paracetamol activated charcoal may be useful after 1 hour of ingestion. Plasma paracetamol levels should be obtained no earlier than 4 hours after ingestion of the paracetamol overdose. Concentrations determined prior to this time are not reliable for assessing potential hepatotoxicity. Measurements of plasma liver enzymes and bilirubin levels, and coagulation studies, should be performed as soon as possible after admission. Blood urea, electrolytes, glucose and blood gases should be obtained. The laboratory measurements are used to monitor hepatic and renal function and electrolyte balance. An ECG should also be performed. Do not delay acetylcysteine therapy while awaiting the results of plasma assays. Once the results become available, treatment may be discontinued if the initial concentration is below nomogram reference line. Do not discontinue acetylcysteine therapy if the initial level is above the reference line and subsequent levels fall below the reference line.
Patient Presenting More Than 15 Hours after Ingestion
Plasma paracetamol, bilirubin, AST, ALT levels and INR should be determined urgently. Patients with INR > 1.3 and/or ALT > 150 should be treated. Further advice should be sought from the New Zealand Poisons Centre.

Anaphylactoid reactions
Anaphylactoid hypersensitivity reactions occur with acetylcysteine, particularly with the initial loading dose. The patient should be carefully observed during the period for signes of an anaphylactoid reaction. Nausea, vomiting, flushing, skin rash, pruritus and urticaria are the most common features, but more severe anaphylactoid reactions have been reported where the patient develops angioedema, bronchospasm, respiratory distress, tachycardia and hypotension. In very rare cases these reactions have been fatal. There is some evidence that patients with a history of atopy and asthma may be at increased risk of developing an anaphylactoid reaction. Most anaphylactoid reactions can be managed by temporarily suspending the acetylcysteine infusion, administering appropriate supportive care, antihistamines and bronchodilators and restarting at a lower infusion rate. Once an anaphylactoid reaction is under control, the infusion can normally be restarted at an infusion rate of 50 mg/kg over 4 hours, followed by the final 150 hour infusion (100 mg/kg over 16 hours).
In patients who have previously had an anaphylactoid reaction acetylcysteine consideration should be given to pre-medication with an H1 antihistamine 15 minutes before starting the acetylcysteine infusion.

Coagulation
Changes in haemostatic parameters have been observed in association with acetylcysteine treatment, some leading to decreased prothrombin time, but most leading to a small increase in prothrombin time (INR). An isolated increase in prothrombin (INR) time up to 1.3 at the end of a 21 hour course of acetylcysteine without an elevated transaminase activity does not require further monitoring or treatment with acetylcysteine.

Fluid and electrolytes
Use with caution in children, patients requiring fluid restriction or those who weigh less than < 40kg because of the risk of fluid overload which may result in hyponatraemia and seizures which may be life threatening (see section 4.2).
Each 10mL ampoule of the infusion concentrate contains 322.6mg sodium. To be taken into consideration with patients on a controlled sodium diet.

Use in Renal/Hepatic Impaired Patients
Caution should be taken when administering acetylcysteine in patients with hepatic or renal failure, since there is little data relating to the effects of acetylcysteine in impaired renal and/or hepatic function. The decision to administer should be passed on a risk/benefit assessment for the individual subject.
In the presence of hepatic failure due to paracetamol overdose the degree of existing liver damage and the possible risk associated with the administration of acetylcysteine should be considered.

Effects on Laboratory Tests
Acetylcysteine may cause a false-positive reaction with reagent dipstick tests for urinary ketones.

Interaction with other medicines and other forms of interaction
There are no known interactions.

Fertility, pregnancy and lactation
Fertility
There was evidence of effects on fertility in male rats given Acetylcysteine at doses up to 68% of the maximum clinical dose, on a body surface area basis. No effects were observed at doses 18% the maximum clinical dose, on a body surface area basis (see section 5.3).
Pregnancy
Category B2
There was no evidence of teratogenicity in limited studies in rats and rabbits following administration of Acetylcysteine during the period of gestation at doses up to 1.2 times the maximum clinical dose, on a body surface area basis. There are no well-controlled studies in pregnant women but experience does not include any positive evidence of adverse effects to the fetus.
Lactation
There was no evidence of adverse effects in a limited study in rats following administration of acetylcysteine during late gestation and lactation at 68% of the maximum clinical dose, on a body surface area basis. It is not known whether acetylcysteine and/or its metabolites are excreted in milk. There are no data on the use of acetylcysteine in lactating women and therefore breastfeeding is not recommended during treatment.
Effects on ability to drive and use machinery
Acetylcysteine is presumed to be safe since it is unlikely to produce an effect that may impair the patient's ability to concentrate and react and therefore not constitute a risk in the ability to drive and use machines.
Undesirable effects
Intravenous administration of acetylcysteine, especially in the large doses needed to treat paracetamol overdose, may result in nausea, vomiting and other gastrointestinal symptoms
Anaphylactoid reactions have been reported following intravenous administration of acetylcysteine. Bronchospasm may occur in conjunction with a generalized anaphylactic reaction. Other symptoms include airway obstruction (bronchospasm), angioedema, dyspnoea, hypotension, chest, tachycardia, urticaria, and injection site reaction (including rash). These reactions occur most commonly either during, or at the end of the loading dose infusion, and may in fact be dose-related. Since these anaphylactic-like reactions usually occur following the loading dose, careful monitoring is recommended.
There have been rare instances of death.
The following adverse effects have been reported:
Blood and lymphatic system disorders: Thrombocythopenia **Immune system disorders:** Anaphylactoid reaction **Metabolism and nutrition disorders:** Acidosis
Psychiatric disorders: Anxiety
Eye disorders: Blurred vision, eye pain
Cardiac disorders: Cyanosis, tachycardia, bradycardia, cardiac arrest, extrasystoles
Vascular disorders: Flushing, hypotension, hypertension, vasodilation
Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory arrest, bronchospasm, coughing, stridor
Gastrointestinal disorders: Vomiting, nausea
Hepatobiliary disorders: Deterioration of liver function
Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash (erythematous and maculopapular), sweating, oedema peripheral
Musculoskeletal and connective tissue disorders: Arthralgia
General disorders and administration site conditions: Malaise, rigors, injection site reaction, chest pain, facial pain, face oedema
Investigations: Raised temperature, changes in prothrombin time (INR) (usually increased).
Hypokalaemia and ECG changes have been noted in patients with paracetamol poisoning irrespective of the treatment given. Monitoring of plasma potassium concentration is therefore recommended.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions.
Overdose
Symptoms
Symptoms following overdose with acetylcysteine have been similar to those of anaphylactoid reactions noted under Undesirable Effects (see section 4.8) but they may be more severe. Hypotension appears to be especially prominent. There is also a theoretical risk of hepatic encephalopathy.
Treatment
There is no specific treatment. General supportive measures should be carried out. It has been suggested that generalised reactions to acetylcysteine can be treated with intravenous injection of an antihistamine, and infusion of acetylcysteine should be temporarily stopped but can be restarted at a lower rate without further reaction.
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766). **Nervous system disorders:** Syncope, generalized seizure
5. PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties Pharmacotherapeutic group: Antidotes, ATC Code: V03AB23 Mechanism of action Paracetamol is metabolised in the liver, mainly by conjugation with glucuronide and sulphate. It is also metabolised by cytochrome P450 to form a reactive, potentially toxic metabolite. This metabolite is normally detoxified by conjugation with hepatic glutathione, to form non-toxic derivatives. In paracetamol overdosage, the glucuronide and sulphate conjugation pathways are saturated, so that more of the toxic metabolite is formed. As hepatic glutathione stores are depleted, this toxic metabolite may limit to hepatocyte proteins, leading to liver cell damage and necrosis. Acetylcysteine is a substrate (GSH) group donor, and may protect the liver from damage by restoring depleted hepatic reduced glutathione levels, or by acting as an alternative substrate for conjugation with, and thus detoxification of, the toxic paracetamol metabolite.
Pharmacokinetic properties
Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine, and is deacetylated in the liver to cysteine, or oxidized to other metabolites such as N- acetylcysteine or N,N-diacetylcystine. The parent compound and metabolites may be present in the plasma either free or protein bound. Renal clearance accounts for about 30% of total body clearance. Following intravenous administration, mean terminal half lives have been calculated to be 1.8h and 5.5h hours respectively for reduced and total acetylcysteine.
Preclinical safety data
Genotoxicity
No evidence of mutagenicity was obtained in limited gene mutation assays with Acetylcysteine. The potential for Acetylcysteine to cause chromosomal damage has not been investigated.
Carcinogenicity
Carcinogenicity assays have not been performed with Acetylcysteine. In rats, no evidence of carcinogenicity was reported following 18 months of daily dietary administration of Acetylcysteine at 60% of the maximum clinical dose, on a body surface area basis.
Reproductive and developmental toxicity
There was evidence of effects on fertility in male rats given Acetylcysteine at doses up to 68% of the maximum clinical dose, on a body surface area basis. No effects were observed at doses 15% the maximum clinical dose, on a body surface area basis.
7. Pharmaceutical Performs
List of excipients
Sodium hydroxide (for pH adjustment) Disodium edetate Water for injections.
Incompatibilities
No data available.
Shelf life
24 months
Once diluted according to directions (see section 4.2), start using within 3 hours.
Special precautions for storage
Store at a temperature not exceeding 25°C. Protect from light.
Nature and contents of container
5ml Type I clear glass ampoules, in packs of 5 ampoules.
Special precautions for disposal
Any unused medicine or waste material should be disposed of in accordance with local requirements.
8. MEDICINE SCHEDULE
Prescription Medicine.
9. SPONSOR
1. DATE OF FIRST APPROVAL
01/01/2004

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