PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM
PARADOTE (Concentrate Solution for Dilution for IV Infusion)

COMPOSITION
Each ml contains acetylcysteine 200 mg i.e. each 10 ml ampoule contains 2 g acetylcysteine as active ingredient.
Other excipients are disodium edetate, sodium hydroxide, water for injection.

PHARMACOLOGICAL CLASSIFICATION
A 32.16 Other.

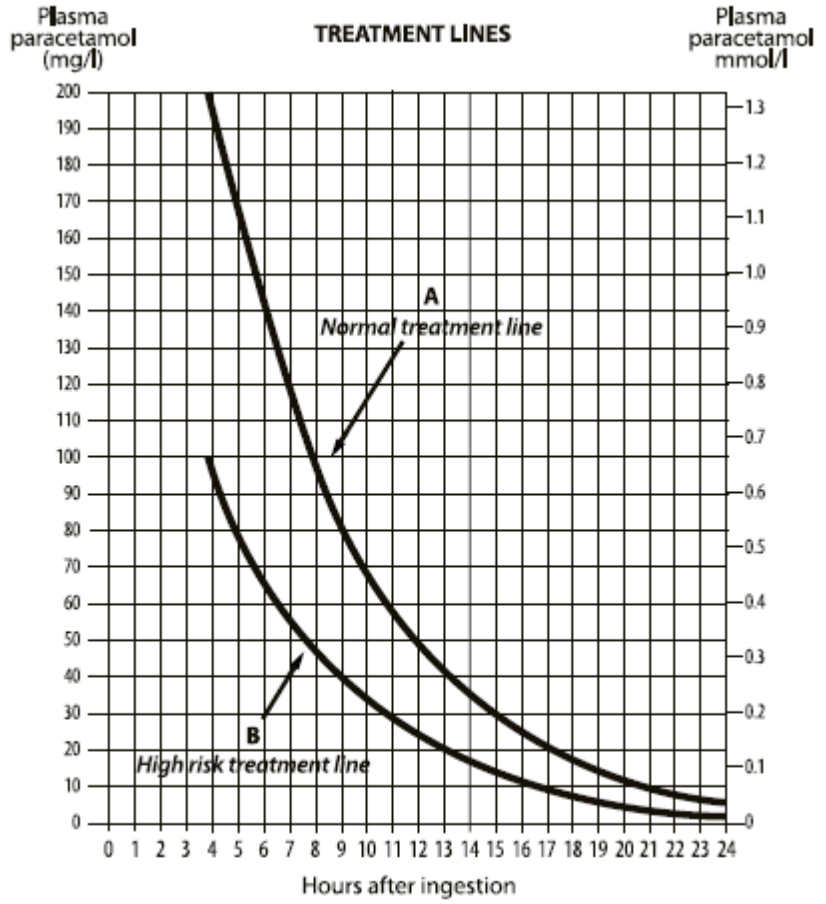
PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Acetylcysteine protects the liver possibly by restoring depleted hepatic-reduced glutathione by acting as an alternative substrate for the toxic paracetamol metabolite, NAPQI (n-acetyl-p-benzo-quinoneimine) following ingestion of a high dose of paracetamol.

INDICATIONS
PARADOTE is indicated for use in paracetamol overdosage.

CONTRAINDICATIONS
Hypersensitivity to acetylcysteine or any excipients in the preparation.

WARNINGS AND SPECIAL PRECAUTIONS
Administer with caution in patients with asthma or a history of bronchospasm. Rash, bronchospasm and anaphylactoid reactions have been reported to occur between 15 and 60 minutes after the start of the infusion. Patient should be monitored for these reactions and treated appropriately (which may include antihistamines and corticosteroids).
Caution should be taken in patients taking medicines that induce liver enzymes, such as anticonvulsant medicine (e.g. phenytoin, phenobarbital, primidone, carbamazepine and rifampicin), and patients who routinely consume alcohol above recommended levels as these patients are believed to be at risk of hepatotoxicity from paracetamol poisoning at lower plasma paracetamol concentrations than other patients. A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with PARADOTE, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.
Those whose plasma paracetamol levels are above the “normal treatment line”, should continue PARADOTE treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.
For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive PARADOTE. Because of lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity
Monitor all patients with significant ingestions for at least ninety six hours.
Hypokalaemia and ECG changes have been noted in patients with paracetamol poisoning irrespective of the treatment given therefore monitoring of plasma potassium concentration is recommended.

Patients suffering from malnutrition, for example, patients with anorexia or AIDS, may have depleted gluthathione reserves and paracetamol overdosage in these patients should be treated as for chronic alcohol consumers or patients taking anticonvulsant therapy (treatment line B – see graph).



Source: From the guidelines agreed by the National Poisons Centres (June 1995)

INTERACTIONS
There are no known interactions.

PREGNANCY AND LACTATION
The safety of PARADOTE in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE
PARADOTE should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.
PARADOTE is for single use only. Any unused portion of the solution/diluted solution should be discarded. Administration should commence within 3 hours after dilution.
PARADOTE must be diluted with one of the following infusion fluids: 5 % dextrose, 0,9 % sodium chloride, 0,3 % potassium chloride with 5 % glucose, or 0,3 % potassium chloride with 0,9 % sodium chloride.
Adults
Initial dose: 150 mg/kg body mass of PARADOTE infused in 200 ml of 5 % dextrose, or 0,9 % sodium chloride, or 0,3 % potassium chloride with 5 % glucose, or 0,3 % potassium chloride with 0,9 % sodium chloride intravenously over 15 minutes, followed by continuous infusion: 50 mg/kg body mass in 500 ml of 5 % dextrose, or 0,9 % sodium chloride, or 0,3 % potassium chloride with 5 % glucose, or 0,3 % potassium chloride with 0,9 % sodium chloride over next 4 hours, followed by 100 mg/kg body mass in 1 litre of 5 %

dextrose, or 0,9 % sodium chloride, or 0,3 % potassium chloride with 5 % glucose, or 0,3 % potassium chloride with 0,9 % sodium chloride over 16 hours.

PARADOTE INTRAVENOUS INFUSION DOSAGE GUIDE

Patients body mass	**Initial**	**Second**	**Third**	**Total PARADOTE**
(kg)	150 mg/kg in 200 ml of infusion dilution fluid over 15 minutes	50 mg/kg in 500 ml of infusion dilution fluid over 4 hours	100 mg/kg in 1 litre of infusion dilution fluid over 16 hours	(ml)
	PARADOTE (ml)	**PARADOTE (ml)**	**PARADOTE (ml)**	
50	37,5	12,5	25	75
60	45,0	15,0	30	90
70	52,5	17,5	35	105
80	60,0	20,0	40	120
90	67,5	22,5	45	135
> 90	0,75x weight	0,25x weight	0,5x weight	1,5x weight

If the patient's body mass is x kg then the infusion volumes of PARADOTE in ml will be:

	Volume per infusion of PARADOTE (ml)	PARADOTE contains 200 mg acetylcysteine in each ml i.e. each 10 ml ampoule contains 2 g acetylcysteine
Initial infusion	0,75x	
Second infusion	0,25x	
Third infusion	0,5x	
Total	1,5x	

Children
The quantity of intravenous fluid used in children should be modified to take into account age and mass.
Compatibility
PARADOTE Injection is a concentrate that must be diluted in dextrose 5 %, or 0,9 % sodium chloride, or 0,3 % potassium chloride with 5 % glucose, or 0,3 % potassium chloride with 0,9 % sodium chloride for intravenous infusion.
The ampoules are for single use only. Discard any unused portion.
Incompatibilities
PARADOTE is incompatible with some metals, including iron, copper and nickel, with rubber, and with oxygen and oxidising substances.
Silicone rubber, and plastic, glass, stainless steel or other unreactive metal is recommended for the use in preparation and administration equipment.
Some antimicrobials including amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with PARADOTE.

SIDE EFFECTS
Immune System disorders
Less frequent: Hypersensitivity or anaphylactoid reactions including bronchospasm, angioedema, rashes and pruritus
Cardiovascular disorders
Frequency unknown: Hypotension or occasionally hypertension may occur, cardiac arrest, ECG changes, tachycardia

Skin and subcutaneous tissue disorders
Frequency unknown: Flushing, sweating
Gastro-intestinal system disorders
Frequency unknown: Nausea, vomiting
Vascular disorders
Less frequent: Fever, syncope
Musculoskeletal disorders
Frequency unknown: Arthralgia
Endocrine disorders
Frequency unknown: Disturbances of liver function; acidosis; hypokalaemia
Nervous system disorders
Less frequent: Convulsions
Eye disorders
Frequency unknown: Blurred vision, puffy eyes, eye pain

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
In overdosage there is a theoretical risk of hepatic encephalopathy. Overdosage has been reported to be associated with effects similar to "anaphylactoid" reactions, but they may be more severe. Treatment is symptomatic and general supportive measures should be carried out.
There is no specific antidote.

IDENTIFICATION
Clear, colourless solution, free from visible particulate matter, for intravenous administration.

PRESENTATION
Clear, colourless Type I glass ampoules containing 200 mg acetylcysteine per ml. Packs of 10 x 10 ml ampoules per outer carton.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
Protect from light.
Store the ampoule in the outer carton until required for use.
Single use only. Any unused portion of the solution/diluted solution should be discarded.
Administration should commence within 3 hours after dilution.
Do not freeze.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
44/32.16/0329

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