HIDONAC®
Acetylcysteine

Composition :
Each bottle of 25 ml contains: Active ingredient: Acetylcysteine 200 mg/ml Excipients: Sodium hydroxide, Disodium edetate, Water for injection.

Pharmaceutical form:
Solution for intravenous infusion

Therapeutic indications:
Voluntary or accidental Paracetamol poisoning

Posology and Method of Administration:
Acetylcysteine must be administered as loading dose, early after paracetamol intake.
Treatment must be continued for at least 72 hours.
In order to avoid the hypersensitive reactions described in the "adverse events". It is advisable to use slow infusion rate. For this purpose the drug is previously diluted with 5 % Glucose or with physiological solution.

Loading Dose: Bolus dose Acetylcysteine 150 mg/Kg in 60 minutes (at least 200 ml in the adult and 50 ml in the child in 5 % glucose or physiological solution).
Subsequence doses: Treatment must be continued with 50 mg/kg doses, at slow infusion rate, every 4 hours for a total of 72 hours of treatment

Loading dose : 150 mg/kg **Duration of perfusion : 60 minutes- minimum volume of dilution : Adults : 200ml/Children : 50 ml**					
Body weight (kg)	20	40	60	80	100
Acetylcysteine mg	3000	6000	9000	12000	15000
HIDONAC ml	15	30	45	60	75
Subsequents doses : 50 mg/kg every 4 hours					
Body weight (kg)	20	40	60	80	100
Acetylcysteine mg	1000	2000	3000	4000	5000
HIDONAC (ml)	5	10	15	20	25

Contra indication :
Hypersenstivity to the active substance or to any of the excipients

Special Warning and precaution for use :
Acetylcysteine should be given by intravenous route under strict medical supervision. The undesirable effects following acetylcysteine intravenous perfusion are more likely to appear if the drug is administered too quickly or in an excessive amount. It is therefore recommended to strictly follow the indications reported under paragraph "Posology".

Anaphylactoid reactions

Anaphylactoid/hypersensitivity reactions occur with acetylcysteine, particularly with the initial loading dose. The patient should be carefully observed during this period for signs of an anaphylactoid reaction. In very rare cases these reactions have been fatal.

Anaphylactoid/hypersensitivity reactions to acetylcysteine usually occur between 15 and 60 minutes after the start of the infusion and, in many cases, symptoms are relieved by stopping the infusion. An antihistamine drug may be necessary, and occasionally corticosteroids may be required.

Most anaphylactoid reactions can be managed by temporarily suspending the acetylcysteine infusion, administering appropriate supportive care 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 16-hour infusion (100 mg/kg over 16 hours)

Bronchial asthma

There is some evidence that patients with a history of atopy and asthma may be at increased risk of developing an anaphylactoid reaction

Patients suffering from bronchial asthma must be closely monitored during therapy. Should bronchospasm occur, acetylcysteine must be stopped immediately and appropriate treatment must be initiated.

Fluid and electrolytes

Caution should be used for administration of antidotal doses in patients with body weight less than 40 kilograms because of the possible risk of fluid overload with subsequent hyponatremia, seizures, and death. It is therefore recommended to strictly follow the indications reported under paragraph “Posology”.

Coagulation

Acetylcysteine administration at antidotal dosages may prolong prothrombin time (decrease in prothrombin index, increase in INR). In any way the monitoring of coagulation factors is advisable particulary in case of liver transplantation

Children and adolescents

The same warnings and precautions reported for adults apply to children and adolescents.

Information on excipients

This medicinal product contains 748 mg sodium (main component of cooking/table salt) in each vial (32.5 mmol), equivalent to 37.4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

A mild smell of sulphur does not indicate an alteration of the product but pertains to the specific nature of the active ingredient.

Interaction with other medicinal products and other forms of interaction:

Drug-Drug interactions

Concurrent administration of nitroglycerin and acetylcysteine has been shown to cause significant hypotension and enhance temporal artery dilation. If concurrent nitroglycerin and acetylcysteine therapy is necessary, patients should be monitored for hypotension, which can be severe, and warned of the possibility of headaches.

Reports of an inactivation of antibiotics resulting from acetylcysteine so far only relate to in-vitro tests in which the relevant substances were mixed directly. Therefore, dissolution of acetylcysteine formulations concomitantly with other drugs is not recommended.

Paediatric population

Interaction studies have only been performed in adults.

Drug-Lab modifications

Acetylcysteine may cause interference with colorimetric assay method for salicylate measurement .

Acetylcysteine may interfere with urine ketone test.

Pregnancy, Lactation and Fertility :

Pregnancy

There are limited clinical data from the use of acetylcysteine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Prior to use in pregnancy, the potential risks should be balanced against the potential benefits.

Breast feeding

There is no information available on excretion in breast milk.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from HIDONAC®therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No data is available on the effect of acetylcysteine on human fertility. Animal studies do not indicate harmful effects with respect to fertility for humans at the recommended doses.

Effects on ability to drive and use machines:

Acetylcysteine has no known influence on the ability to drive and use machines.

Undesirable effects :

Summary of safety profile

Adverse reactions to acetylcysteine are mainly anaphylactoid, hypersensitivity in nature; urticaria, rash, pruritus, and dyspnoea are the most frequent features.

More serious anaphylactoid / hypersensitivity reactions have been reported where the patient develops angioedema, bronchospasm, tachycardia and hypotension.

Case reports of fatalities with intravenous acetylcysteine as antidote for paracetamol overdose have been reported very rarely.

Tabulated list of adverse reactions

The following adverse reactions were reported during post-marketing experience; their frequency is not known (cannot be estimated from the available data).

System Organ Class	**Adverse reactions - Frequency Not known (*)**
Immune system disorders	Anaphylactic shock Anaphylactic reaction, Anaphylactoid reaction, Hypersensitivity
Cardiac disorders	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm Dyspnoea
Gastrointestinal disorders	Vomiting Nausea
Skin and subcutaneous tissue disorders	Angioedema Urticaria Flushing Rash Pruritus
General disorders and administration site conditions	Face oedema
Investigations	Blood pressure decreased Prothrombin time prolonged

(*) not known (cannot be established from the available data).

Description of selected adverse reactions

In very rare cases, the occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has been reported in temporal connection with the administration of acetylcysteine.
In most cases at least one co-suspect drug more probably involved in triggering the reported mucocutaneous syndrome could be identified.
Because of this, medical advice should be sought straight away if any new changes to the skin or mucous membranes occur, and acetylcysteine should be stopped immediately.

A decrease in platelet aggregation in the presence of N-acetylcysteine has been confirmed by various investigations. The clinical significance has not yet been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Overdose :
Symptoms
Overdose of acetylcysteine has been reported to be associated with effects similar to the 'anaphylactoid' reactions noted in section 4.8 (Undesirable Effects), but they may be more severe
Treatment
Overdose treatment is based on immediate discontinuation of the infusion administration and symptomatic treatment and resuscitation. There are no specific antidotal treatments; acetylcysteine is dialyzable.
Paediatric population
The same symptoms and treatment apply to the paediatric population.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties

Pharmacotherapeutic group: Antidotes, acetylcysteine ATC code V03AB23
The molecular structure of acetylcysteine enables it to easily cross cell membranes. Inside the cell, acetylcysteine is deacetylated, thus yielding L-cysteine, an amino acid indispensable for glutathione (GSH) synthesis. Acetylcysteine exerts in addition an indirect antioxidant effect through its role as GSH precursor. GSH is a highly reactive tripeptide, ubiquitously spread in the various tissues of animal organisms, which is essential for the maintenance of the cell functional capacity as well as morphological integrity. In fact, it is the most important intracellular defence mechanism against oxidizing radicals, both exogenous and endogenous, and several cytotoxic substances, including paracetamol.

Paracetamol, exerts its cytotoxic action through progressive GSH impoverishment 30. Acetylcysteine plays its primary importance role by maintaining of adequate GSH levels, thus contributing to the cellular protection. Therefore, acetylcysteine represents a specific antidote for paracetamol poisoning.
Acetylcysteine reduces the hepatic toxicity of NAPQI (n-acetyl-p-benzo-quinone-imine), the highly reactive intermediate metabolite following ingestion of a high dose of paracetamol, by the following mechanisms.

- Acetylcysteine acts as a precursor for the synthesis of glutathione and, therefore, maintains cellular glutathione at a level sufficient to inactivate NAPQI. This is thought to be the main mechanism by which acetylcysteine acts in the early stages of paracetamol toxicity, with benefit seen principally in patients treated within 8-10 hours of the overdose.
- When acetylcysteine treatment is begun more than 8 to 10 hours after paracetamol overdose, its efficacy in preventing hepatotoxicity (based on serum indicators) declines progressively with further lengthening of the overdose-treatment interval (the time between paracetamol overdose and start of treatment).
- Acetylcysteine has been shown to still be effective when infusion is started at up to 12 hours after paracetamol ingestion, when most of the analgesic will have been metabolised to its reactive metabolite. At this stage, acetylcysteine is thought to act by reducing oxidised thiol groups in key enzymes.

There is now evidence that it can still be beneficial when given up to 24 hours after overdose. At this late stage of paracetamol hepatotoxicity, acetylcysteine's beneficial effects may be due to its ability to improve systematic haemodynamics and oxygen transport, although the mechanism by which this may occur has yet to be determined.

Pharmacokinetic properties

Absorption

After intravenous infusion, using the 20-hour modelling, the plasma levels of acetylcysteine reached 300 -900 mg/L few minutes after the start of the infusion, decreasing to 11 - 90mg/L at the end of the infusion.

Distribution

Acetylcysteine in rats is distributed both in the non-metabolized and the metabolized (active) form, and can mainly be found in the liver, kidneys, lungs and bronchial secretions. The volume of distribution of acetylcysteine ranges from 0.33 to 0.47 L/kg. Protein binding is about 50% four hours after the dose and decreases to 20% at 12 h. There is no information on whether acetylcysteine crosses the blood-brain barrier or whether it is excreted in breast milk. Acetylcysteine crosses the placenta.

Biotransformation

Acetylcysteine undergoes rapid and extensive metabolism in the gut wall and liver following oral administration.

The resulting compound, cysteine, is considered to be an active metabolite Following this stage of transformation, acetylcysteine and cysteine share the same metabolic route. Renal clearance may account for about 30% of total body clearance. Following oral administration, the terminal half-life of total acetylcysteine is 6.25 h.

Elimination

After a single intravenous dose of acetylcysteine, plasma concentration of total acetylcysteine shows a poli-exponential decline with a terminal half-life (T1/2) of 5.6 hours. Renal clearance has been defined at 0,11 litre/h/kg and it may account for about 30% of total body clearance.

Hepatic Insufficiency

In subjects with severe hepatic insufficiency, associated with alcoholic cirrhosis (**n = 7**, Child-Pugh score 7-13) or biliary cirrhosis primary or secondary (**n = 2**, Child-Pugh score 5-7), elimination half-life (T1/2) increased by 80% while the elimination decreased by 30%, as compared to the control group.

Renal Insufficiency

There is no pharmacokinetics data available in patients with renal insufficiency.

Preclinical safety data:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

High dose treatment in pregnant rats and rabbits revealed no evidence of impaired female fertility or harm to the foetus due to acetylcysteine.

Treatment of rats for 28 weeks with acetylcysteine at the dose level of 250 mg/kg oral dose proved to be completely devoided of systemic toxicity on male and female Animals and produced no untoward effects on male fertility.

Shelf-Life and Storage conditions:
3 years in the original packaging and properly stored at temperature below 30°C, as solution for phleboclysis.
Mixing HIDONAC with other drugs is not advised. Since NAC can react chemically with rubber, iron,copper, etc., it advisable to use glass or plastic materials.

DO NOT USE THIS PRODUCT PAST IT EXPIRY DATE : THIS DATE IS LOCATED IN THE BOX
KEEP OUT THE REACH OF CHILDREN
HARUS DENGAN RESEP DOKTER

Packing : Box, 1 bottle contains 25 ml

Manufactured by:	**Imported by:**	**Marketed by:**
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