SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HIDONAC 5 g/25 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 25 ml vial contains:

Active ingredient

Acetylcysteine g 5

3. PHARMACEUTICAL FORM

Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accidental or voluntary acetaminophen poisoning.

4.2 Posology and method of administration

The antidotal treatment should be started as soon as possible by administration of the attack dose, and should be prosecuted for at least 72 hours.

The infusion is to be performed slowly, in order to minimize the possible risk of hypersensitivity reactions, as described under paragraph "Undesirable effects". To this aim, the medicine should be previously diluted with 5% glucose solution or physiological saline.

Attack dose

Start the treatment with an attack dose of 150 mg/kg body weight, to be perfused throughout 60 minutes by previous dilution (in at least 200 ml for adults and 50 ml in paediatric-age subjects).

Subsequent doses

The treatment should be continued for 72 hours, by slow infusion of 50 mg/kg body weight every 4 hours, by previous product dilution.

ATTACK DOSE: 150 mg/kg Perfusion time 60' Minimum dilution volume: adults 200 ml - children 50 ml					
Body weight in kg	20	40	60	80	100
NAC mg	3000	6000	9000	12000	15000
HIDONAC ml	15	30	45	60	75
SUBSEQUENT DOSES: 50 mg/kg every 4 hours					
Body weight in kg	20	40	60	80	100
NAC mg	1000	2000	3000	4000	5000
HIDONAC	5	10	15	20	25

4.3 Contraindications

Hypersensitivity to the product ingredients or to other chemically strictly related substances.

4.4 Special warnings and precautions for use

Patients suffering from bronchial asthma or with previous episodes of bronchospasm should be closely monitored during therapy; if bronchospasm appears, a symptomatic therapy should be applied.

The intravenous administration requires an appropriate surveillance within a hospital environment.

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".

Acetylcysteine administration at antidotal dosages may reduce prothrombin time, even if it is unclear whether such effect represents an interference of analytical type or is rather the expression of a NAC biological action. In any case it is necessary to carefully control the coagulation factors in the treated patients, especially with a view to a possible liver transplantation.

Moreover, NAC may interfere with salicylate dosage (colorimetric method) as well as plasma and urinary ketone detection (nitroprusside test).

The presence of a sulfurous odour is not indicative of a product alteration, but pertains to the specific nature of therein contained active ingredient.

KEEP OUT OF THE REACH OF CHILDREN

4.5 Interactions with other medicinal products and other forms of interaction

Acetylcysteine interactions with some antibiotics have been reported, however appearing of no relevance in terms of antidotal treatment.

4.6 Pregnancy and lactation

Teratology studies performed with acetylcysteine in animals and the available limited clinical experience, did not evidence any teratogenic effect.

The risks of hepatic injury for the mother and foetus as a consequence of intoxications, are probably much higher than the potential risks related to the treatment, therefore pregnancy should not be considered as a contraindication to the drug use.

Lactation should be discontinued in any case after the toxic episode.

4.7 Effects on ability to drive and use machines

There are no assumptions nor evidences that the drug may affect the attention capacity and reaction times.

4.8 Undesirable effects

The product use by intravenous route may be followed by an anaphylactic reaction or other hypersensitivity reactions such as urticaria, angioedema, bronchospasm, nausea, vomiting, arterial hypotension, tachycardia, dizziness, fever.

Probably pseudoallergic reactions are implied, based on a mechanism of histamine release, that may require an emergency symptomatic treatment.

4.9 Overdose

Overdose symptoms are superimposable to the undesirable effects. Their treatment involves the drug discontinuation and the application of symptomatic and/or resuscitative measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

N-acetyl-L-cysteine (NAC), active ingredient of HIDONAC, is a cysteine derivative endowed with a nucleophilic free thiol group (-SH), able to directly interact with electrophilic groups of oxidizing radicals.
Its molecular structure allows NAC to easily cross cell membranes. Inside the cell, NAC is deacetylated, thus yielding L-cysteine, an amino acid indispensable for glutathione synthesis.
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, as it represents the most important intracellular defence mechanism against oxidizing radicals, both exogenous and endogenous, and several cytotoxic substances. Thanks to its properties as glutathione precursor and antioxidant agent, NAC is used as an alternative substrate and favours cellular protection against noxious agents that, through a progressive GSH impoverishment, would be able to fully exert their cytotoxic action, as in acetaminophen poisoning, that may lead to liver failure, encephalopathy and death.
Acetylcysteine administration, by increasing glutathione supplies, allows to face its increased needs, thus preventing liver injuries. The antidotal treatment efficacy is the higher, the earlier the treatment is started.

5.2 Pharmacokinetic properties

After oral administration, peak plasma concentrations are reached after 1 hour and bioavailability is lower than 10% of the administered dose, due to an intense hepatic first-pass effect. The drug is found in blood mainly as disulfide dimer (N,N'-diacetylcystine) or mixed with other thiols having low molecular weight or with proteins. The elimination half-life after repeated administration, both by oral and intravenous route, is 5-6 hours. Elimination occurs mainly by urinary excretion and the main metabolite is, when no intoxication is present, inorganic sulfate. Anyway, in intoxicated patients, NAC derivatives in urine depend mostly on the toxic substance and its possible combination with the drug.

5.3 Preclinical safety data

Acetylcysteine is characterized by a particularly reduced toxicity. The LD_{50} is higher than 10 g/kg by oral route both in mice and rats, whilst by intravenous route it amounts to 2.8 g/kg in rats and 4.6 g/kg in mice. In long-term treatments, the 1 g/kg/day oral dose has been well tolerated in rats for 12 weeks. The oral administration of 300 mg/kg/day in dogs for a period of one year, induced no toxic reactions. The high-dose treatment in pregnant rats and rabbits during the organogenesis period, did not cause the birth of dysmorphic offspring.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Sodium hydroxide, sodium edetate, water for injectable preparations.

6.2 Incompatibilities

It is recommended not to mix other medicines with HIDONAC solution.
Acetylcysteine may interact with rubber and metals (such as iron, nickel, copper): therefore the use of glass or plastic materials is recommended.

6.3 Shelf-life

Three years.
The expiry date refers to the product in its intact and original package and properly stored.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Type I glass vial with butyl rubber stopper
Box containing 1 vial.

6.6 Special precautions for disposal and handling

The diluted solution for intravenous infusion is stable for 24 hours.

7. MARKETING AUTHORIZATION HOLDER

ZAMBON ITALIA s.r.l.
Via Lillo del Duca, 10 – 20091 Bresso (MI)
Tax number n. 03804220154

8. MARKETING AUTHORIZATION NUMBER(S)

M.A. : 032268017

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 14/5/1997
Date of renewal: 26/5/2007

10. DATE OF (PARTIAL) REVISION OF THE TEXT

26/5/2007