HIDONAC SOLUTION FOR IV INFUSION
(5G/25ML)

Intravenous Use
N-Acetylcysteine

FORMULATION
Each ml of solution contains acetylcysteine 200mg.

PRODUCT DESCRIPTION
Colourless glass vials, containing a clear, colourless or very slightly pink-violaceous solution with a slightly sulphurous odour.

PHARMACOLOGY AND PHARMACOKINETICS PROPERTIES
Pharmacology
Pharmacotherapeutic group: Antidotes, ATC code: V03AB23
N-acetyl-L-cysteine (NAC), active ingredient of HIDONAC® is a cysteine derivative provided with a free thiol (-SH) nucleophilic group which is able to interact directly with the electrophilic group of the oxidant radicals. Due to its molecular structure, NAC can easily cross the cellular membranes. Inside the cell, NAC is deacetylated to L-cysteine, an amino acid required for the synthesis of glutathione (GSH). GSH is a highly reactive tripeptide, found ubiquitously in various tissues of animals and it is essential for the maintenance of functional capacity as well as cellular morphological integrity, since it represents the most important protective endocellular mechanism against oxidant radical, either exogenous or endogenous, as well as towards numerous cytotoxic substances.
Due to its antioxidant property and its effectiveness in promoting the synthesis of glutathione, NAC is used as a substrate contributing to the cellular protection from harmful agents which, through progressive GSH depletion, would be able to express their cytotoxic action as in the case of paracetamol poisoning that may lead to hepatic failure, encephalopathy and death.
NAC administration is effective in the prevention of liver damage maintaining an adequate GSH level. The efficacy of the treatment is most likely to occur when it is started early.

Toxicology
NAC has been evaluated to have low toxicity. After intravenous administration, the LD50 is 2.8g/kg in rat and 4.5g/kg in mouse. After oral administration, the LD50 is more than 10g/kg both in rat and mouse. During the repeated administration studies, the dose of 1g/kg/die by oral route for 12 weeks has been well tolerated by rat. In dogs, no toxic reactions have been observed after oral administration of 300mg/kg/die for one year. No teratogenic effect was observed in the offspring of pregnant rats and rabbits when treated with high dose of NAC during organogenesis period.

Pharmacokinetics
The tmax was approximately 1 hour after oral administration. The bioavailability by the oral route was less than 10% of the dose administered. This finding does not mean that the drug is poorly absorbed but that extensive first-pass metabolism of the drug occurs in the liver. In plasma, NAC is found as N, N'diacetylcysteine and mixed disulfides with other thiols or of low molecular weight or with proteins. The elimination half-life was 5-6 hours after intravenous administration. NAC is mainly excreted in the urine. The main urinary metabolite of NAC is the inorganic sulphate. However, in intoxicated patients, the NAC derivatives in the urine depend mainly on the toxic substance and its possible complexes with the drug.

INDICATIONS
Voluntary or accidental paracetamol poisoning

DOSAGE AND ADMINISTRATION
The product must be previously diluted with 5% glucose or with physiological solution according to recommended dosage schedule. Sodium chloride 0.9% can be used if glucose 5% is not suitable.
The reconstituted solution is stable for 24 hours at a temperature not exceeding 25°C. Acetylcysteine must be administered as loading dose early after paracetamol intake.
The full treatment course with N-acetylcysteine is 3 consecutive bags of intravenous infusion. The doses must be administered one after the other, with no interruptions between infusions. The patient must receive a total dose of 300 mg/kg of body weight for 21 hours.

Adults
Administration
– Weigh the patient to establish the correct weight band.
– Use the adult dosage table to establish the appropriate volume of N-acetylcysteine (bottle volume) to add to the infusion fluid in each of the 3 infusion periods.

First infusion
Add the appropriate volume of N-acetylcysteine to inject to 200 ml of infusion fluid to be administered over 1 hour.

Second infusion
Add the appropriate volume of N-acetylcysteine to inject to 500 ml of infusion fluid to be administered over the following 4 hours.

Third infusion
Add the appropriate volume of N-acetylcysteine to inject to 1 litre of infusion fluid to be administered over the following 16 hours.
When calculating the dose for obese patients, the maximum weight to consider is 110 kg. The dose must be calculated using the patient's current weight.

Adult dosage table

Prescription of N-acetylcysteine in adults (each bottle = 200 mg/ml of N-Acetylcysteine)			Circle the appropriate weight, dose and volume			
Regimen	First infusion		Second infusion		Third infusion	
Infusion fluid	200 ml of Glucose 5% solution or of sodium chloride 0.9% solution		500 ml of glucose 5% solution or of sodium chloride 0.9% solution		1000 ml of glucose 5% solution or of sodium chloride 0.9% solution	
Duration of the infusion	1 hour		4 hours		16 hours	
Drug dose	150 mg/kg of N- Acetylcysteine		50 mg/kg N-Acetylcysteine		100 mg/kg N-Acetylcysteine	
Patient weight[1]	Bottle volume[2]	Infusion rate	Bottle volume[2]	Infusion rate	Bottle volume[2]	Infusion rate
kg	ml	ml/h	ml	ml/h	ml	ml/h
40-49	34	234	12	128	23	64
50-59	42	242	14	129	28	64
60-69	49	249	17	129	33	65
70-79	57	257	19	130	38	65
80-89	64	264	22	131	43	65
90-99	72	272	24	131	48	66
100-109	79	279	27	132	53	66
>110 - maximum dose	83	283	28	132	55	66

[1] Dose calculations are based on the average weight in each band. If the patient weighs less than 40 kg, use the paediatric dosage table.
[2] The bottle's volume has been rounded to the nearest whole number.

Children
Children must be treated with the same dose and the same regimen as adults. However, the quantity of intravenous fluid used must be modified considering age and weight, because an overdose of fluids is potentially dangerous.
The doses must be administered one after the other, using an appropriate intravenous pump.

Preparation and administration of paediatric infusions
– Weigh the child to establish the correct weight band.
– Use the table to find the total infusion volume required for each dose according to the child's weight and prepare the solution following the instructions below

The full treatment course with N-acetylcysteine is 3 consecutive bags of intravenous infusion.

First infusion
– Prepare a 50 mg/ml solution diluting every 10 ml of Hidonac (200 mg/ml) with 30 ml of glucose 5% or sodium chloride 0.9% until a 40 ml total volume is obtained.
– Prepare the volume appropriate for the child's weight.
– The dose is infused for 1 hour at the infusion rate shown in the table.

Second infusion
– Prepare a 6.25 mg/ml solution diluting every 10 ml of Hidonac (200 mg/ml) with 310 ml of glucose 5% or sodium chloride 0.9% until a 320 ml total volume is obtained.
– Prepare the volume appropriate for the child's weight.
– The dose is infused for 4 hours at the infusion rate shown in the table.

Third infusion
– Prepare a 6.25 mg/ml solution diluting every 10 ml of Hidonac (200 mg/ml) with 310 ml of glucose 5% or sodium chloride 0.9% until a 320 ml total volume is obtained.
– Prepare the volume appropriate for the child's weight.
– The dose is infused for 16 hours at the infusion rate shown in the table.

E.g., for a child weighing 12 kg, the first infusion should be 38 ml administered at a rate of 38 ml/h in 1 hour; the second infusion should be 100 ml administered at a rate of 25 ml/h in 4 hours and the third infusion should be 208 ml administered at a rate of 13ml/h in 16 hours.

Paediatric dosage table

Paediatric prescription of N-acetylcysteine (each bottle = 200 mg/ml of N-Acetylcysteine)			Circle the appropriate weight, dose and volume			
Regimen	First infusion		Second infusion		Third infusion	
Infusion	50 mg/ml for 1 hour		6.25 mg/ml for 4 hours		6.25 mg/ml for 16 hours	
Infusion rate	3 ml/kg/h		2 ml/kg/h		1 ml/kg/h	
Patient weight[1]	Infusion rate	Total infusion volume[2]	Infusion rate	Total infusion volume[2]	Infusion rate	Total infusion volume[2]
kg	ml/h	ml	ml/h	ml	ml/h	ml
1	3	3	2	8	1	16
2	6	6	4	16	2	32
3	9	9	6	24	3	48
4	12	12	8	32	4	64
5	15	15	10	40	5	80
6	18	18	12	48	6	96
7	21	21	14	56	7	112
8	24	24	16	64	8	128
9	27	27	18	72	9	144
10-14	38	38	25	100	13	208
15-19	53	53	35	140	18	288

Scale 1:1

Paediatric prescription of N-acetylcysteine (each bottle = 200 mg/ml of N-Acetylcysteine)			Circle the appropriate weight, dose and volume			
Regimen	First infusion		Second infusion		Third infusion	
Infusion	50 mg/ml for 1 hour		6.25 mg/ml for 4 hours		6.25 mg/ml for 16 hours	
Infusion rate	3 ml/kg/h		2 ml/kg/h		1 ml/kg/h	
Patient weight[1]	Infusion rate	Total infusion volume[2]	Infusion rate	Total infusion volume[2]	Infusion rate	Total infusion volume[2]
kg	ml/h	ml	ml/h	ml	ml/h	ml
20-24	68	68	45	180	23	368
25-29	83	83	55	220	28	448
30-34	98	98	65	260	33	528
35-39	113	113	75	300	38	608

[1] Dose calculations are based on the average weight in each band. If the patient weighs more than 40 kg, use the adult dosage table.
[2] Figures have been rounded to the nearest whole number.

CONTRAINDICATIONS
Known hypersensitivity to the drug or to other chemically related substances. Contraindicated in children under 2 years of age.

WARNINGS AND PRECAUTIONS
Intravenous administration requires careful supervision and must be performed in hospital settings.
Undesirable effects are more likely to appear as a result of the intravenous administration of N-Acetylcysteine if the drug administered rapidly or an excessive amount is used.

Hypersensitivity Reactions
Serious acute hypersensitivity reactions during NAC administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous NAC for paracetamol overdose and occurred soon after initiation of the infusion (see ADVERSE EVENTS). If a severe hypersensitivity reaction occurs, immediately stop the infusion of NAC and initiate appropriate treatment.

Acute flushing and erythema of the skin may occur in patients receiving NAC intravenously. These reactions usually occur 15 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of NAC. If a reaction to NAC involves more than simply flushing and erythema of the skin, it should be treated as a hypersensitivity reaction.
Management of less severe hypersensitivity reactions should be based upon the severity of the reaction and include temporary interruption of the infusion and/or administration of antihistaminic drugs. The NAC infusion may be carefully restarted after treatment of the hypersensitivity symptoms has been initiated; however, if the hypersensitivity reaction returns upon re-initiation of treatment or increases in severity, NAC should be discontinued and alternative patient management should be considered.

Bronchial asthma
There is some evidence that patients with a history of atopy and asthma may be at high risk of developing an anaphylactoid reaction. Patients affected by bronchial asthma or with a history of bronchospasm episodes must be closely supervised during therapy. If bronchospasm occurs, the administration of N-acetylcysteine must be stopped immediately and symptoms must be treated.

Fluids and electrolytes
In the case of administration of antidote doses to patients weighing less than 40kg, there is the possible risk of administering an excessive dose of liquids, leading to hyponatraemia, seizures and death.
The instructions in section 'DOSAGE AND ADMINISTRATION' should therefore be followed carefully.

Coagulation
The administration of N-acetylcysteine at antidote doses may increase prothrombin time (reduction of prothrombin index, increased INR), although it is not clear if this effect is an interference with analysis results or is the expression of a biological action of NAC. Regardless, the coagulation factors in treated patients should be carefully evaluated, especially for purposes related to liver transplant.

Children and adolescents
The same warnings and precautions listed for adults also apply to children and adolescents.

Important information on some of the excipients
This medicinal product contains 748 mg of sodium per bottle (32.5 mmoles), equivalent to 37.4% of the maximum daily intake recommended by the WHO for an adult (2 g of sodium). When opening a bottle of Hidonac, a sulphurous odour may be perceived; this is typical of the active substance contained in the medicine and does not mean the product is altered.

DRUG INTERACTIONS
Interactions between acetylcysteine and antibiotics have been reported. However, these are not remarkable when NAC is administered as treatment for paracetamol poisoning. Mixing HIDONAC® with other drugs is not advised. Since NAC can react chemically with rubber, iron, copper etc., it is advisable to use glass or plastic material.
The concomitant administration of nitroglycerine and N-acetylcysteine has been shown to cause significant hypotension and leads to the dilation of the temporal artery.
If it is necessary to administer nitroglycerine and N-acetylcysteine at the same time, patients must be monitored for the appearance of hypotension (which can be severe) and informed about the possible development of headaches.
The information available on the interaction between antibiotics and Nacetylcysteine refers to tests in vitro, in which the two substances were mixed, showing a decrease in antibiotic activity. However, as a precaution, antibiotics should not be mixed with the N-acetylcysteine solution.

Paediatric population
Interaction studies were only carried out in adults.

Drug - laboratory test interaction
N-acetylcysteine may interfere with the colourimetric method for the measurement of salicylates. N-acetylcysteine may interfere with the test for the measurement of ketones in the urine.

USE DURING PREGNANCY AND LACTATION
Pregnancy
The clinical information related to the administration of N-acetylcysteine during pregnancy is limited. With regard to reproductive toxicity, studies on animals have not highlighted direct or indirect toxic effects on pregnancy, embryonic or foetal development, natal or post-natal development. Prior to use in pregnancy, the potential risks should be balanced against the potential benefits.

Breast-feeding
There is no available information on excretion in maternal milk. A risk to the baby cannot be excluded. During breast-feeding, the medicine must only be used after carefully assessing the risk/benefit ratio.

Fertility
No data on the effect that N-acetylcysteine has on human fertility is available. Animal studies indicate that there are no damaging effects on human fertility at the recommended doses.

ADVERSE EVENTS
Summary of the safety profile
The adverse events most frequently associated with the administration of NAC are of hypersensitivity and anaphylactoid nature: urticaria, rash and itching are the most common symptoms.
For use as an antidote, more serious anaphylactoid/ hypersensitivity reactions have been reported that include angioedema, bronchospasm, tachycardia and hypotension. Very rarely there have been reports of fatalities due to an intravenous overdose of acetylcysteine used as an antidote for the overdose of paracetamol.

Immune System Disorders:
Anaphylactic/ anaphylactoid reaction.

Skin and Subcutaneous Tissue Disorders:
Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects.

Table of adverse reactions
The following adverse events have been reported during post-marketing experience (the frequency cannot be estimated from the available data).

MedDRA 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, itching
General disorders and administration site conditions	Facial oedema
Diagnostic examinations	Decrease in blood pressure, increased prothrombin time

(*) not known (cannot be estimated from the available data)

In very rare cases, severe skin reactions occurred when taking N-acetylcysteine, such as Stevens-Johnson syndrome and Lyell syndrome.
Although in most cases at least one other drug was identified as being more likely to be involved in the development of such muco-cutaneous syndromes, patients should seek medical advice and immediately suspend treatment with Nacetylcysteine if muco-cutaneous alterations occur.
Some studies have confirmed a reduction in platelet aggregation when taking Nacetylcysteine. The clinical significance of such findings has yet to be determined.

OVERDOSE
Cases of overdose were characterised by similar symptomatology but more severe than those observed in cases of adverse events. In case of overdose, treatment must be suspended. Management of overdose is based on symptomatic treatment and/or resuscitation. There are no specific antidote treatments; NAC can be dialysed.

Paediatric population
The same symptoms and treatments are associated with the paediatric population.

STORAGE
Store in the original packaging at a temperature not exceeding 30°C. SHELF-LIFE: 3 years

AVAILABILITY SOLUTION FOR INTRAVENOUS INFUSION
HIDONAC® Solution for Intravenous Infusion, 5g/25ml (20%) is supplied in glass bottles of 25 ml.

DO NOT USE BEYOND THE EXPIRY DATE
KEEP OUT OF THE REACH OF CHILDREN

Manufacturer:
Alfasigma S.p.A.
Via Enrico Fermi, 1, 65020 Alanno (PE), Italy

Product Registration Holder/Importer:
EP Plus Group Sdn Bhd (429571D)
Block C-3-1, Plaza Mont Kiara, No.2, Jalan Kiara, Mont Kiara, 50480, Kuala Lumpur.

Date of Revision: August 2023

Zambon

A_HQ_2023000053-1
42007262 AW17-0024 (CP. 8/10)

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Zambon S.p.A
Via Lillo del Duca 10
20091 Bresso / Milano

CODICE / ITEM: A_HQ_2023000053-1	ED. / VERSION N.: N/A	DATA / DATE: 02/10/2023
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COD. FORNITORE / SUPPLIER CODE: 42007262	PHARMA CODE: 3216 (LSSLSSLSSSL)	EDGE CODE: N/A
STABILIMENTO / PLANT: ALFASIGMA	PACKAGING LINE: LINEA FLC	
CHANGE DESCRIPTION: NUOVO TESTO / NEW TEXT		

PRODOTTO / BRAND: **LFT - HIDONAC INJ 1 FLC 5G/25 ML MY linea FLC**
REV MOCKUP APPROVATO - DATA: **N/A**
ARTWORK REV: **REV2**
CONFORME AL MASTER LAYOUT - NOTE: **AW17-0024**
COLORI / COLORS NO: **2**
BRAILLE: **N/A**
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LATO STAMPA BIANCA/VOLTA (SIDE PRINT FRONT/REAR): **LATO VOLTA / BACK SIDE**
FONT/CORPO MIN./INTERLINEA (FONT/MIN. SIZE/SPACING): **HELVETICA NEUE**
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ISTRUZIONI FORNITORE / SUPPLIER INSTRUCTION:
CARTA 40 gr
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Scale 1:1