ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of cysteamine (as mercaptamine bitartrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard Capsule
White, opaque hard capsules with CYSTA 50 on the body and RECORDATI RARE DISEASES on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

CYSTAGON is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

4.2 Posology and method of administration

CYSTAGON treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.

The goal of therapy is to keep leucocyte cystine levels below 1 nmol hemicystine/mg protein. White blood cell (WBC) cystine levels should therefore be monitored to adjust the dose. The WBC levels should be measured 5 to 6 hours after dosing and should be checked frequently when initiating therapy (e.g. monthly) and every 3-4 months when on a stable dose.

- *For children up to age 12 years,* CYSTAGON dosing should be on the basis of body surface area (g/m^2/day). The recommended dose is 1.30 g/m^2/day of the free base divided four times daily.
- *For patients over age 12 and over 50 kg weight,* the recommended CYSTAGON dose is 2 g/day, divided four times daily.

Starting doses should be 1/4 to 1/6 of the expected maintenance dose, increased gradually over 4-6 weeks to avoid intolerance. The dose should be raised if there is adequate tolerance and the leucocyte cystine level remains >1 nmol hemicystine/mg protein. The maximum dose of CYSTAGON used in clinical trials was 1.95 g/m^2/day.
The use of doses higher than 1.95 g/m^2/day is not recommended (see section 4.4).

Digestive tolerance of cysteamine is improved when the medicinal product is taken just after or with food.

In children who are at risk of aspiration, aged approximately 6 years and under, the hard capsules should be opened and the content sprinkled on food. Experience suggests that foods such as milk, potatoes and other starch based products seem to be appropriate for mixing with the powder. However, acidic drinks, e.g. orange juice, should generally be avoided as the powder tends not to mix well and may precipitate out.

Patients on dialysis or post-transplantation:
Experience has occasionally shown that some forms of cysteamine are less well tolerated (i.e.leading to more adverse events) when patients are on dialysis. A closer monitoring of the leucocyte cystine levels is recommended in these patients.

Patients with hepatic insufficiency:
Dose adjustment is not normally required; however, leucocyte cystine levels should be monitored.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
The use of CYSTAGON is contra-indicated during breast-feeding. CYSTAGON should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (see section 4.6 and section 5.3 as it is teratogenic in animals.

CYSTAGON is contraindicated in patients who have developed hypersensitivity to penicillamine.

4.4 Special warnings and precautions for use

CYSTAGON therapy must be initiated promptly after confirmation of the diagnosis of nephropathic cystinosis to achieve maximum benefit.

Nephropathic cystinosis must have been diagnosed by both clinical signs and biochemical investigations (leucocyte cystine measurements).

Cases of Ehlers-Danlos like syndrome and vascular disorders on elbows have been reported in children treated with high doses of different cysteamine preparations (cysteamine chlorhydrate or cystamine or cysteamine bitartrate) mostly above the maximal dose 1.95 g/m^2/day. These skin lesions were associated with vascular proliferation, skin striae and bone lesions.
It is therefore recommended to monitor regularly skin and to consider X-ray examinations of the bone as necessary. Self-examination of the skin by the patient or the parents should also be advised. If any similar skin or bone abnormalities appear, it is recommended to decrease the dose of CYSTAGON. The use of doses higher than 1.95g/m^2/day is not recommended (see sections 4.2 and 4.8).

Monitoring of blood cell count is recommended on a regular basis.

Oral cysteamine has not been shown to prevent eye deposition of cystine crystals. Therefore, where cysteamine ophthalmic solution is used for that purpose, its usage should continue.

In contrast to phosphocysteamine, CYSTAGON does not contain phosphate. Most patients will already be receiving phosphate supplements and the dose of these may need to be altered when CYSTAGON is substituted for phosphocysteamine.

Intact CYSTAGON hard capsules should not be administered to children under the age of approximately 6 years due to risk of aspiration (see section 4.2).

Do not swallow the desiccant canister found in the bottle

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed
CYSTAGON can be administered with electrolyte and mineral replacements necessary for management of the Fanconi syndrome as well as vitamin D and thyroid hormones. Indomethacin and CYSTAGON have been used simultaneously in some patients. In cases of patients with kidney transplants, anti-rejection treatments have been used with cysteamine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of cysteamine bitartrate in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenesis (see section 5.3). The potential risk for humans is unknown. The effect on pregnancy of untreated cystinosis is also unknown.
Therefore, CYSTAGON should not be used during pregnancy, particularly during the first trimester, unless clearly necessary.
If a pregnancy is diagnosed or planned, the treatment should be carefully reconsidered and the patient must be advised of the possible teratogenic risk of cysteamine.

Breast-feeding
CYSTAGON excretion in human's milk is unknown. However, due to the results of animal studies in breast-feeding mothers and neonates (see section 5.3), breast-feeding is contraindicated in women taking CYSTAGON.

4.7 Effects on ability to drive and use machines

CYSTAGON has minor or moderate influence on the ability to drive and use machines
CYSTAGON may cause drowsiness. When starting therapy, patients should not engage in potentially hazardous activities until the effects of the medicinal product on each individual are known.

4.8 Undesirable effects

Approximately 35% of patients can be expected to experience adverse reactions. These mainly involve the gastrointestinal and central nervous systems. When these effects appear at the initiation of cysteamine therapy, temporary suspension and gradual reintroduction of treatment may be effective in improving tolerance.

Reported adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriouness

Investigations	*Common*: Liver function tests abnormal
Blood and lymphatic system disorders	*Uncommon*: Leukopenia
Nervous system disorders	*Common*: Headache, encephalopathy *Uncommon*: Somnolence, convulsions
Gastrointestinal disorders	*Very common*: Vomiting, nausea, diarrhoea *Common*: Abdominal pain, breath odour, dyspepsia, gastroenteritis *Uncommon*: Gastrointestinal ulcer
Renal and urinary disorders	*Uncommon*: Nephrotic syndrome
Skin and subcutaneous tissue disorders	*Common*: Skin odour abnormal, rash *Uncommon*: Hair colour changes, skin striae, skin fragility (molluscoid pseudotumor on elbows)
Musculoskeletal and connective tissue disorders	*Uncommon*: Joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture, scoliosis.
Metabolism and nutrition disorders	*Very common*: Anorexia
General disorders and administration site conditions	*Very common*: Lethargy, pyrexia *Common*: Asthenia
Immune system disorders	*Uncommon*: Anaphylactic reaction
Psychiatric disorders	*Uncommon*: Nervousness, hallucination

Cases of nephrotic syndrome have been reported within 6 months of starting therapy with progressive recovery after treatment discontinuation. In some cases, histology showed a membranous glomerulonephritis of the renal allograft and hypersensitivity interstitial nephritis.

Cases of Ehlers-Danlos like syndrome and vascular disorders on elbows have been reported in children chronically treated with high doses of different cysteamine preparations (cysteamine chlorhydrate or cystamine or cysteamine bitartrate) mostly above the maximal dose 1.95 g/m^2/day.
In some cases, these skin lesions were associated with vascular proliferation, skin striae and bone lesions first seen during an X-ray examination. Bone disorders reported were genu valgum, leg pain and hyperextensive joints, osteopenia, compression fractures, and scoliosis.
In cases where histopathological examination of the skin was performed, the results suggested angioendotheliomatosis.
One patient subsequently died of acute cerebral ischemia with marked vasculopathy.
In some patients, the skin lesions on elbows regressed after CYSTAGON dose reduction.
Cysteamine mechanism of action by interfering with the cross-linking of collagen fibers has been postulated (see section 4.4).

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 listed in Appendix V.

4.9 Overdose

An overdose of cysteamine may cause progressive lethargy.

Should overdosage occur, the respiratory and cardiovascular systems should be supported appropriately. No specific antidote is known. It is not known if cysteamine is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism product, ATC code: A16AA04.

Normal individuals and heterozygous subjects for cystinosis have white cell cystine levels of < 0.2, and usually below 1 nmol hemicystine/mg protein, respectively. Individuals with nephropathic cystinosis have elevations of white cell cystine above 2 nmol hemicystine/mg protein

Cysteamine reacts with cystine to form the mixed disulfide of cysteamine and cysteine.
The mixed disulfide is then exported from the lysosomes by an intact lysine transport system. The decrease in leucocyte cystine levels is correlated to the cysteamine plasma concentration over the six hours following the administration of CYSTAGON.

The leucocyte cystine level reaches its minimum (mean (± sd) value: 1.8 ± 0.8 hours) slightly later than the peak plasma cysteamine concentration (mean (± sd) value: 1.4 ± 0.4 hours) and returns to its baseline level as the plasma cysteamine concentration decreases at 6 hours post-dose.

In one clinical study, baseline white cell cystine levels were 3.73 (range 0.13 to 19.8) nmol hemicystine/mg protein and were maintained close to 1 nmol hemicystine/mg protein with a cysteamine dose range of 1.3 to 1.95 g/m^2/day.
An earlier study treated 94 children with nephropathic cystinosis with increasing doses of cysteamine to attain white cell cystine levels of less than 2 nmol hemicystine/mg protein 5 to 6 hours post-dose,

and compared their outcome with an historical control group of 17 children treated with placebo. The principal efficacy measurements were serum creatinine and calculated creatinine clearance and growth (height). The mean white cell cystine level attained during treatment was 1.7 ± 0.2 nmol hemicystine/mg protein. Among cysteamine patients, glomerular function was maintained over time. Placebo treated patients, in contrast, experienced a gradual rise in serum creatinine. Patients on treatment maintained growth as compared to untreated patients. However, growth velocity did not increase enough to allow patients to catch up the normal for their age. Renal tubular function was not affected by treatment. Two other studies have shown similar results.

In all studies, patient response was better when treatment was started at an early age with good renal function.

5.2 Pharmacokinetic properties

Following a single oral dose of cysteamine bitartrate equivalent to 1.05 g of cysteamine free base in healthy volunteers, the mean (± sd) values for the time to peak and peak plasma concentration are 1.4 (± 0.5) hours and 4.0 (± 1.0) µg/ml, respectively. In patients at steady state, these values are 1.4 (± 0.4) hours and 2.6 (± 0.9) µg/ml, respectively, after a dose ranging from 225 to 550 mg.
Cysteamine bitartrate (CYSTAGON) is bioequivalent to cysteamine hydrochloride and phosphocysteamine.

The *in vitro* plasma protein binding of cysteamine, which is mostly to albumin, is independent of plasma drug concentration over the therapeutic range, with a mean (± sd) value of 54.1 % (± 1.5). The plasma protein binding in patients at steady state is similar: 53.1 % (± 3.6) and 51.1 % (± 4.5) at 1.5 and 6 hours post-dose, respectively.

In a pharmacokinetic study performed in 24 healthy volunteers for 24 hours, the mean estimate (± sd) for the terminal half-life of elimination was 4.8 (± 1.8) hours.

The elimination of unchanged cysteamine in the urine has been shown to range between 0.3 % and 1.7% of the total daily dose in four patients; the bulk of cysteamine is excreted as sulphate.

Very limited data suggest that cysteamine pharmacokinetic parameters may not be significantly modified in patients with mild to moderate renal insufficiency. No information is available for patients with severe renal insufficiency.

5.3 Preclinical safety data

Genotoxicity studies have been performed: although in published studies using cysteamine, induction of chromosome aberrations in cultured eukaryotic cell lines has been reported, specific studies with cysteamine bitartrate did not show any mutagenic effects in the Ames test or any clastogenic effect in the mouse micronucleus test.

Reproduction studies showed embryofoetotoxic effects (resorptions and post-implantation losses) in rats at the 100 mg/kg/day dose level and in rabbits receiving cysteamine 50 mg/kg/day. Teratogenic effects have been described in rats when cysteamine is administered over the period of organogenesis at a dose of 100 mg/kg/day.
This is equivalent to 0.6 g/m^2/day in the rat, which is less than half the recommended clinical maintenance dose of cysteamine, i.e. 1.30 g/ m^2/day. A reduction of fertility was observed in rats at 375 mg/kg/day, a dose at which body weight gain was retarded. At this dose, weight gain and survival of the offspring during lactation was also reduced. High doses of cysteamine impair the ability of lactating mothers to feed their pups. Single doses of the drug inhibit prolactin secretion in animals. Administration of cysteamine in neonate rats induced cataracts.
High doses of cysteamine, either by oral or parenteral routes, produce duodenal ulcers in rats and mice but not in monkeys. Experimental administration of the drug causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the drug is unknown.

No carcinogenic studies have been conducted with CYSTAGON.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
microcrystalline cellulose,
pregelatinized starch,
magnesium stearate/sodium lauryl sulfate,
colloidal silicon dioxide,
croscarmellose sodium
Capsule shell:
gelatin,
titanium dioxide,

black ink on hard capsules containing E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

HDPE bottles of 100 and 500 hard capsules. A desiccant unit containing black activated carbon and silica gel granules is included in the bottle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/039/001 (100 hard capsules per bottle), EU/1/97/039/002 (500 hard capsules per bottle).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 1997.
Date of latest renewal: 23 June 2007.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg of cysteamine (as mercaptamine bitartrate)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard Capsule
White, opaque hard capsules with CYSTAGON 150 on the body and RECORDATI RARE DISEASES on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

CYSTAGON is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

4.2 Posology and method of administration

CYSTAGON treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.

The goal of therapy is to keep leucocyte cystine levels below 1 nmol hemicystine/mg protein. White blood cell (WBC) cystine levels should therefore be monitored to adjust the dose. The WBC levels should be measured 5 to 6 hours after dosing and should be checked frequently when initiating therapy (e.g. monthly) and every 3-4 months when on a stable dose.

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- *For patients over age 12 and over 50 kg weight,* the recommended CYSTAGON dose is 2 g/day, divided four times daily.

Starting doses should be 1/4 to 1/6 of the expected maintenance dose, increased gradually over 4-6 weeks to avoid intolerance. The dose should be raised if there is adequate tolerance and the leucocyte cystine level remains >1 nmol hemicystine/mg protein. The maximum dose of CYSTAGON used in clinical trials was 1.95 g/m^2/day.
The use of doses higher than 1.95 g/m^2/day is not recommended (see section 4.4).

Digestive tolerance of cysteamine is improved when the medicinal product is taken just after or with food.

In children who are at risk of aspiration, aged approximately 6 years and under, the hard capsules should be opened and the content sprinkled on food. Experience suggests that foods such as milk, potatoes and other starch based products seem to be appropriate for mixing with the powder. However, acidic drinks, e.g. orange juice, should generally be avoided as the powder tends not to mix well and may precipitate out.

Patients on dialysis or post-transplantation:
Experience has occasionally shown that some forms of cysteamine are less well tolerated (i.e. leading to more adverse events) when patients are on dialysis. A closer monitoring of the leucocyte cystine levels is recommended in these patients.

Patients with hepatic insufficiency:
Dose adjustment is not normally required; however, leucocyte cystine levels should be monitored.

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The use of CYSTAGON is contra-indicated during breast-feeding. CYSTAGON should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (see section 4.6 and section 5.3), as it is teratogenic in animals.

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In contrast to phosphocysteamine, CYSTAGON does not contain phosphate. Most patients will already be receiving phosphate supplements and the dose of these may need to be altered when CYSTAGON is substituted for phosphocysteamine.

Intact CYSTAGON hard capsules should not be administered to children under the age of approximately 6 years due to risk of aspiration (see section 4.2).

Do not swallow the desiccant canister found in the bottle.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed
Interactions with other medicines have not been studied. CYSTAGON can be administered with electrolyte and mineral replacements necessary for management of the Fanconi syndrome as well as vitamin D and thyroid hormones. Indomethacin and CYSTAGON have been used simultaneously in some patients. In cases of patients with kidney transplants, anti-rejection treatments have been used with cysteamine.

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Pregnancy
There are no adequate data from the use of cysteamine bitartrate in pregnant women. Studies in animals have shown reproductive toxicity, including teratogenesis (see section 5.3). The potential risk for humans is unknown. The effect on pregnancy of untreated cystinosis is also unknown.
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Breast-feeding
CYSTAGON excretion in human's milk is unknown. However, due to the results of animal studies in breast-feeding mothers and neonates (see section 5.3), breast-feeding is contra-indicated in women taking CYSTAGON.

4.7 Effects on ability to drive and use machines

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4.9 Overdose

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Should overdosage occur, the respiratory and cardiovascular systems should be supported appropriately. No specific antidote is known. It is not known if cysteamine is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism product, ATC code: A16AA04.

Normal individuals and heterozygous subjects for cystinosis have white cell cystine levels of < 0.2, and usually below 1 nmol hemicystine/mg protein, respectively. Individuals with nephropathic cystinosis have elevations of white cell cystine above 2 nmol hemicystine/mg protein

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The mixed disulfide is then exported from the lysosomes by an intact lysine transport system. The decrease in leucocyte cystine levels is correlated to the cysteamine plasma concentration over the six hours following the administration of CYSTAGON.

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An earlier study treated 94 children with nephropathic cystinosis with increasing doses of cysteamine to attain white cell cystine levels of less than 2 nmol hemicystine/mg protein 5 to 6 hours post-dose,

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In all studies, patient response was better when treatment was started at an early age with good renal function.

5.2 Pharmacokinetic properties

Following a single oral dose of cysteamine bitartrate equivalent to 1.05 g of cysteamine free base in healthy volunteers, the mean (± sd) values for the time to peak and peak plasma concentration are 1.4 (± 0.5) hours and 4.0 (± 1.0) µg/ml, respectively. In patients at steady state, these values are 1.4 (± 0.4) hours and 2.6 (± 0.9) µg/ml, respectively, after a dose ranging from 225 to 550 mg.
Cysteamine bitartrate (CYSTAGON) is bioequivalent to cysteamine hydrochloride and phosphocysteamine.

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In a pharmacokinetic study performed in 24 healthy volunteers for 24 hours, the mean estimate (± sd) for the terminal half-life of elimination was 4.8 (± 1.8) hours.

The elimination of unchanged cysteamine in the urine has been shown to range between 0.3 % and 1.7% of the total daily dose in four patients; the bulk of cysteamine is excreted as sulphate.

Very limited data suggest that cysteamine pharmacokinetic parameters may not be significantly modified in patients with mild to moderate renal insufficiency. No information is available for patients with severe renal insufficiency.

5.3 Preclinical safety data

Genotoxicity studies have been performed: although in published studies using cysteamine, induction of chromosome aberrations in cultured eukaryotic cell lines has been reported, specific studies with cysteamine bitartrate did not show any mutagenic effects in the Ames test or any clastogenic effect in the mouse micronucleus test.

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High doses of cysteamine, either by oral or parenteral routes, produce duodenal ulcers in rats and mice but not in monkeys. Experimental administration of the drug causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the drug is unknown.

No carcinogenic studies have been conducted with CYSTAGON.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
microcrystalline cellulose,
pregelatinized starch,
magnesium stearate/sodium lauryl sulfate,
colloidal silicon dioxide,
croscarmellose sodium
Capsule shell:
gelatin,
titanium dioxide,
black ink on hard capsules containing E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

HDPE bottles of 100 and 500 hard capsules. A desiccant unit containing black activated carbon and silica gel granules is included in the bottle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52 avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/039/003 (100 hard capsules per bottle), EU/1/97/039/004 (500 hard capsules per bottle).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 1997.

Date of latest renewal: 23 June 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Recordati Rare Diseases
Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux, France

or

Recordati Rare Diseases
Eco River Parc
30, rue des Peupliers
F-92000 Nanterre
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON CYSTAGON 50 mg x 100 hard capsules
OUTER CARTON CYSTAGON 50 mg x 500 hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 50 mg hard capsules
Cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of cysteamine (as mercaptamine bitartrate) .

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules (with a desiccant unit in the bottle)
500 hard capsules (with a desiccant unit in the bottle)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant canister found in the bottle

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52 avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/039/001 – 100 hard capsules
EU/1/97/039/002 – 500 hard capsules

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystagon 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON CYSTAGON 150 mg x 100 hard capsules
OUTER CARTON CYSTAGON 150 mg x 500 hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 150 mg hard capsules
Cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg of cysteamine (as mercaptamine bitartrate) .

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules (with a desiccant unit in the bottle)
500 hard capsules (with a desiccant unit in the bottle)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant canister found in the bottle

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/039/003 – 100 hard capsules
EU/1/97/039/004 – 500 hard capsules

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystagon 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL CYSTAGON 50 mg x 100 hard capsules
BOTTLE LABEL CYSTAGON 50 mg x 500 hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 50 mg hard capsules
Cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of cysteamine (as mercaptamine bitartrate) .

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules (with a desiccant unit in the bottle)
500 hard capsules (with a desiccant unit in the bottle)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant canister found in the bottle

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/039/001 – 100 hard capsules
EU/1/97/039/002 – 500 hard capsules

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL CYSTAGON 150 mg x 100 hard capsules
BOTTLE LABEL CYSTAGON 150 mg x 500 hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 150 mg hard capsules
Cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg of cysteamine (as mercaptamine bitartrate) .

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules (with a desiccant unit in the bottle)
500 hard capsules (with a desiccant unit in the bottle)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant canister found in the bottle

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the container tightly closed in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52, Avenue du Général de Gaulle
F-92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/039/003 – 100 hard capsules
EU/1/97/039/004 – 500 hard capsules

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cystagon 50 mg Hard Capsules
Cystagon 150 mg Hard Capsules
cysteamine bitartrate (mercaptamine bitartrate)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What CYSTAGON is and what it is used for

Cystinosis is a metabolic disease called 'nephropathic cystinosis' which is characterized by an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Cystine build up causes kidney damage and excretion of excess amounts of glucose, proteins and electrolytes. Different organs are affected at different ages.

CYSTAGON is prescribed to manage this rare inherited disorder. CYSTAGON is a medicine that reacts with cystine to decrease its level within the cells.

2. What you need to know before you use CYSTAGON

Do not use CYSTAGON
- if you -or your child- are allergic to cysteamine bitartrate or penicillamine or any of the other ingredients of this medicine (listed in section 6).
- If you are pregnant, this is particularly relevant during the first trimester
- if you are breast-feeding.

Warnings and precautions
- When your or your child's disorder has been confirmed by leucocyte cystine measurements, the therapy with CYSTAGON must be started as soon as possible.
- A few cases of skin lesions on elbows like little hard lumps have been reported in children treated with high doses of different cysteamine preparations. These lesions were associated with skin striae and bone lesions such as fracture and bone deformities, and with laxity of joints. Your doctor could require a regular physical and X-ray examination for the skin and the bones to control the effects of the medicinal product. Self examination of your or your child's skin is recommended. If any skin or bone abnormalities appear, please inform your doctor immediately.
- Your doctor could require controlling the blood cell count on a regular basis.
- CYSTAGON has not been shown to prevent cystine crystals accumulating in the eye. Where cysteamine ophthalmic solution has been used for that purpose, its usage should continue.

- In contrast to phosphocysteamine, another active substance close to cysteamine bitartrate, CYSTAGON does not contain phosphate. You may already be receiving phosphate supplements and the dose of these may need to be changed when CYSTAGON is substituted for phosphocysteamine.
- To avoid any risk of aspiration in the lungs, the capsules should not be given to children under the age of approximately 6 years.
- Do not swallow the desiccant canister found in the bottle

Other medicines and CYSTAGON
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

CYSTAGON with food and drink
For children under approximately six years of age, the hard capsule may be opened and the contents sprinkled on food (e.g. milk, potatoes or starch based foods) or mixed in formula. Do not add to acidic drinks e.g. orange juice. Consult the doctor for complete directions.

Pregnancy
You should not use CYSTAGON if you are pregnant. Please consult your doctor if you plan to become pregnant.

Breast-feeding
CYSTAGON must not be used during breast-feeding.

Driving and using machines
CYSTAGON may cause some drowsiness. When starting therapy, you or your child should not engage in potentially hazardous activities until the effects of the drug are well known.

3. How to use CYSTAGON

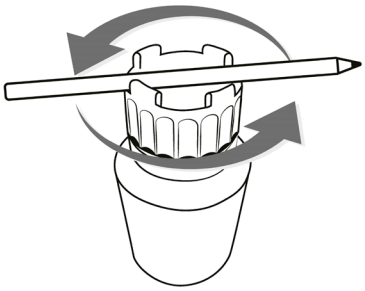
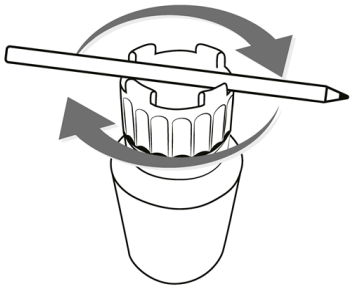
Always use this medicine exactly as your doctor or your child's doctor has told you. Check with your doctor if you are not sure.
The dose of CYSTAGON prescribed for you or your child will depend on your or your child's age and weight.
For children up to age 12 years, the dose will be based on the body size (surface area), the usual dose being 1.30 g/m^2 of body surface area per day.
For patients over age 12 and over 50 kg weight, the usual dose is 2g/day.
In any case the usual dose should not exceed 1.95 g/m^2/day.
CYSTAGON should be taken or given only by mouth and exactly as your or your child's doctor directs. In order for CYSTAGON to work correctly, you must do the following:
- Follow your doctor's directions exactly. Do not increase or decrease the amount of medicine without your doctor's approval.
- Hard capsules should not be given to children under approximately six years of age because they may not be able to swallow them and they may choke. For children under approximately six years of age, the hard capsule may be opened and the contents sprinkled on food (e.g. milk, potatoes or starch based foods) or mixed in formula. Do not add to acidic drinks e.g. orange juice. Consult the doctor for complete directions.
- Your or your child's medical treatment may include, in addition to CYSTAGON, one or more supplements to replace important electrolytes lost through the kidneys. It is important to take or give these supplements exactly as instructed. If several doses of the supplements are missed or weakness or drowsiness develops, call the doctor for instructions.
- Regular blood tests to measure the amount of cystine inside white blood cells are necessary to help determine the correct dose of CYSTAGON. Your or your child's doctor will arrange for the blood tests to be done. Regular blood and urine tests to measure the levels of the body's important electrolytes are also necessary to help your or your child's doctor correctly adjust the doses of these supplements.

CYSTAGON should be taken 4 times a day, every 6 hours, preferably just after or with food. It is important to take the dose as close to every 6 hours as possible.

Treatment with CYSTAGON should continue indefinitely, as instructed by your doctor.

To easily open and close the Cystagon bottle, please follow the instructions below:

Directions for opening and closing the container

OPEN	CLOSE
	
To Open Place pen or similar object between the raised sections of the lid and turn in the direction shown (anticlockwise)	**To Close** Place pen or similar object between the raised sections of the lid and turn in the direction shown (clockwise)

If you use more CYSTAGON than you should:
You should contact your or your child's doctor or the hospital emergency department immediately if more medicine has been taken than has been prescribed, drowsiness develops .

If you forget to take CYSTAGON:
If a dose of medicine is missed, it should be taken as soon as possible. However if it is within two hours of the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

CYSTAGON may cause some people to become drowsy or less vigilant than they are normally. Make sure you know how you or your child reacts to this medicine before doing anything that could be dangerous if not alert.

The following side effects were reported as follows: very common (occurring in at least one in 10 patients), common (occurring in at least one in 100 patients), uncommon (occurring in at least one in1,000 patients), rare (occurring in at least one in 10,000 patients), very rare (occurring in at least one in 100,000 patients).

- Very common: vomiting, nausea, diarrhoea, loss of appetite, fever and sensation of sleep

- Common: abdominal pain or discomfort, unpleasant breath and body odour, skin eruption, gastroenteritis, fatigue, headache, encephalopathy (brain disorder) and liver function test abnormalities.

- Uncommon: skin striae, skin lesion (little-hard lumps on elbows), joint laxity, leg pain, bone fracture, scoliosis (deviation of the vertebral column), bone deformity and fragility, hair discoloration, severe allergic reaction, somnolence, fits, nervousness, hallucination, decrease in white blood cells, gastrointestinal ulcer manifested by bleeding in the digestive tract and effect on the kidney manifested by swelling of the extremities and weight gain**.**

Since some of these side effects are serious, ask your or your child's doctor to explain their warning signs.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CYSTAGON

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C and keep the container tightly closed in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CYSTAGON contains
- The active substance is cysteamine bitartrate (mercaptamine bitartrate). Each hard capsule of CYSTAGON 50 mg contains 50 mg of cysteamine (as mercaptamine bitartrate) Each hard capsule of CYSTAGON 150 mg contains 150 mg of cysteamine (as mercaptamine bitartrate)
- The other ingredients are microcrystalline cellulose, starch, pregelatinized, magnesium stearate/sodium lauryl sulphate, colloidal silicon dioxide, croscarmellose sodium, capsule shells: gelatin, titanium dioxide, black ink on hard capsules (E172).

What CYSTAGON looks like and contents of the pack
Hard Capsules
- Cystagon 50 mg: white, opaque hard capsules with CYSTA 50 on the body and RECORDATI RARE DISEASES on the cap.
Bottles of 100 or 500 hard capsules. All pack sizes may be not marketed.

- Cystagon 150 mg: white, opaque hard capsules with CYSTAGON 150 on the body and RECORDATI RARE DISEASES on the cap.
Bottles of 100 or 500 hard capsules. All pack sizes may be not marketed.

Marketing Authorisation Holder
Recordati Rare Diseases
Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux
France

Manufacturer
Recordati Rare Diseases

Tour Hekla
52, avenue du Général de Gaulle
F-92800 Puteaux
France

or

Recordati Rare Diseases
Eco River Parc
30, rue des Peupliers
F-92000 Nanterre
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Франция

Česká republika
Recordati Rare Diseases
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Francie

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Sverige

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Rootsi

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.