Physician's Prescribing Information

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 cysteamine 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.

- *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 special 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
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.

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 contra-indicated 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 seriousness

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 the 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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 $\pm$ 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,
croscarmellose sodium,
colloidal silicon dioxide.
Capsule shell:
gelatin,
titanium gelatin. black ink on hard capsules

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 hard capsules. A desiccant unit containing black activated carbon and silica gel granules is included in the bottle.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MANUFACTURER

Recordati Rare Diseases
Puteaux
France

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St.,
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Israel

Registration Number 152-28-34049

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