4. Clinical aspects

Introduction

The applicants own data are limited to a pharmacokinetic study conducted in 12 healthy volunteers following administration of single dose and repeated doses of betaine and to safety data gathered in EU and the USA. Clinical efficacy is based on 202 reports retrieved from literature search.

GCP

According to the applicant, the studies followed all ethical guidelines in practice at the time of conduct of the studies. No issues regarding GCP aspects have been identified during the review of the dossier.

Pharmacokinetics

The absolute bioavailability of betaine has not been determined. In healthy adult volunteers (age between 21 to 49 years), after a single oral dose of betaine (50 mg/kg), absorption was rapid (tmax = 0.9 ± 0.3 hours and a Cmax = 0.9 ± 0.2 mM). Betaine was rapidly distributed into a relatively large volume (V/F = 1.3 l/kg), with a slow elimination rate (mean half life = 14 h, mean total body clearance, CL/F, = 84 ml/h/kg), renal clearance being negligible (5% of total body clearance), assuming 100% bioavailability. After a repeated dose regimen of 100 mg/kg/day for 5 days, the absorption kinetics did not change but the distribution half-life was prolonged significantly (up to 36 h), indicating saturable transport and redistribution processes. The pharmacokinetic data of homocystinuric patients on long-term betaine supplementation are very similar to those of healthy volunteers. This demonstrates that differences in betaine kinetics are most probably due to betaine depletion in untreated homocystinuria and are only meaningful for the initial treatment.

There is a possibility of chemical interactions with certain foodstuffs and antibiotics. These interactions, although they have not been formally investigated, may be clinically significant. Based on in vitro data, betaine might interact with amino acids mixtures and drugs like vigabatrin and GABA analogues. As mentioned in the section 4.4 of the SPC, to minimize the risk of potential drug interactions, it is advisable to leave 30 minutes between the intake of betaine and amino acids mixtures and/or medicinal products containing vigabatrin and GABA analogues.

Differences in pharmacockinetics related to gender, age or race or the comorbidity have not been systematically studied. However, considering the nature and prevalence of the disease this was considered to be acceptable.

Pharmacodynamics

The pharmacodynamics of betaine are based on a review of four published studies in 161 healthy volunteers, one study with a sequential increase of dose in 34 volunteers and three studies with repeated doses and on published data in patients.

The mechanism of action of betaine in hyperhomocystinaemia has sufficiently been established. No additional data was required. Betaine supplementation appears to be effective in lowering plasma tHcy (plasma total homocysteine) concentrations in healthy subjects and in patients with homocystinuria. Betaine supplementation also seems to improve the metabolic abnormalities in the central nervous compartment of patients with homocystinuria. The extent of the effect on plasma tHcy is dependent on the absolute degree of hyperhomocysteinemia, being higher in severe hyperhomocysteinemia.

In CBS- (Cystathionine beta-synthase) deficiency the risk of an excessive accumulation of methionine and associated adverse events should be considered.

The SPC sections 4.4 and 4.5 adequately reflect the potential risk of drug interactions.

Clinical efficacy

Clinical efficacy is based on 202 reports retrieved from literature search. Most cases were reported as individual case reports and about 25% cases were pooled as groups of patients. Some of these patients have been reported several times, i.e. as a case report at diagnosis, as a case report later in life, and in a pooled review. Verified data are available in 140 patients, in which individual biochemical or clinical features as well as dose and duration of betaine therapy, and pre-existing or concomitant therapies were documented.

Biochemical efficacy of betaine treatment in homocystinuria using the widely accepted surrogate marker of plasma homocysteine appears to have been demonstrated in the published reports submitted for this application.

Regarding clinical efficacy no data from systematic studies are available. In addition a variety of doses and co-treatments have been used. Several forms of bias might have influenced the results. Therefore the clinical efficacy of betaine treatment is more difficult to assess than the biochemical efficacy. No clear improvement was expected from further studies, especially considering the heterogeneous patient population in question. Also the limited available data indicated at least an efficacy of betaine in preventing further disease progress. FUMs were not regarded to improve the situation either.

It is therefore considered that the data submitted showing biochemical efficacy and the associated improvements regarding the various disease symptoms after betaine therapy compared with historical data of untreated patients provide sufficient evidence of betaine's effectiveness. However, it is likely that due to the multiple nature of therapy (dietary, pharmaceutical, supportive) in these patients, there may be an element of overestimation in the clinical effects of betaine treatment. The seemingly late detection in symptoms leads to irreversible damage, especially to the nervous system and connective tissue. Such damage cannot be corrected by further therapy. These issues are reflected in the section 5.1 of the SPC.

The available clinical data do not allow correlating dosage and clinical efficacy. There is no evidence of development of tolerance. For example, there were no reported rises in blood levels of homocysteine during long-term betaine treatment.

In conclusion, although there are only a few systematic studies available, data presented in this application appear to show both biochemical and clinical benefits of betaine supplementation in the management of homocystinuria.

Clinical safety

In general, adverse effects seen with betaine therapy appear to be not serious and are mainly related to the gastrointestinal system. Study OMC-BETR-1 indicates that these AEs are dose-related. Betaine has already been supplemented in many patients over many years. Many of the available data concerning safety of betaine have been obtained from neonates, infants, and children of different age groups. In this regard, no age-related difference in toxicity of betaine has been observed. However data from controlled trials are sparse.

The occurrence of five cases of potentially life-threatening cerebral oedema while receiving the usual dose of betaine raises concern. It is not clear whether these reported cases occurred due to accumulation of methionine, or betaine, or both, or independently of therapy. In this regard special attention should be paid in patients with poor dietary control of hypermethioninemia. It is necessary to advise prescribing physicians to monitor methionine plasma concentrations especially in patients with CBS-deficiency receiving betaine and to pay attention to early clinical signs of cerebral oedema. Plasma methionine level should be monitored, at start of treatment and periodically thereafter. The plasma methionine concentrations should be kept below 1000 μM. If any symptoms of cerebral oedema like morning headaches with vomiting or visual changes appear, plasma methionine level and

compliance to the diet should be checked and treatment with Cystadane interrupted. If symptoms of cerebral oedema recur after re-introduction of treatment then betaine therapy should be discontinued indefinitely. This information is reflected in the SPC.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities (see the section referred below in the Product Information)
Cerebral oedema	routine pharmacovigilance patient registry to gather data on demographics, drug utilisation and safety profile.	**4.4 Special warnings and precautions for use** Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting betaine therapy (see section 4.8). Complete recovery was seen after treatment discontinuation: - Plasma methionine level should be monitored, at start of treatment and periodically thereafter. The plasma methionine concentrations should be kept below 1000 µM. - If any symptoms of cerebral oedema like morning headaches with vomiting and/or visual changes appear, plasma methionine level and compliance to the diet should be checked and treatment with Cystadane interrupted. - If symptoms of cerebral oedema recur after re-introduction of treatment then betaine therapy should be discontinued indefinitely. **4.8 Undesirable effects** Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting betaine therapy, with complete recovery after treatment discontinuation. High increases in plasma methionine

		levels in a range from 1,000 to 3,000 µM were noted in these patients. As cerebral oedema has also been reported in patients with hypermethioninemia, secondary hypermethioninemia due to betaine therapy has been postulated as a possible mechanism of action. For specific recommendations, refer to section 4.4.
Limited number of patients treated with betaine	routine pharmacovigilance patient registry to gather data on demographics, drug utilisation and safety profile	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Efficacy

The data submitted showing biochemical efficacy and the associated improvements regarding the various disease symptoms after betaine therapy compared with historical data of untreated patients provide sufficient evidence of betaine's effectiveness. Betaine in the treatment of homocystinuria has been investigated in different age groups and both male and females. No differences in pharmacokinetics or dose-response have been reported. In addition, long-term treatment demonstrated constant effects over time. However, it is likely that due to the multiple nature of therapy (dietary, pharmaceutical, supportive) in these patients, there may be an element of overestimation in the clinical effects of betaine treatment.

Since no patient has been treated with betaine alone, it is difficult to distinguish the clinical benefits attributable to betaine from those affected by other treatment options. Nonetheless, the addition of betaine to pre-existing therapies appears to lower homocysteine plasma concentrations and leads to improved disease symptoms in a substantial group of patients, particularly those with cardiovascular symptoms. Homocysteine plasma concentrations are generally accepted as a surrogate marker for the severity of disease. Therefore, it can be considered that betaine offers benefit to patients with homocystinuria. It is however important to emphasise that betaine is no substitute for the currently available therapies such as relevant vitamin or dietary preparations. In cases where biochemical markers are controlled by restricted diet and vitamin supplementation (B6, B12, folate) no advantage is to be expected for betaine co-treatment. Even though the dosage is not critical, its use should be clinically and, where appropriate, also biochemically monitored by an experienced physician on a regular basis.

Safety

With regards to safety, betaine appears to be well tolerated. Many of the available data concerning safety of betaine have been obtained from neonates, infants, and children of different age groups.

In general, adverse effects seen with betaine therapy appeared to be not serious and were mainly related to the gastrointestinal system. The occurrence of cases of potentially life-threatening cerebral oedema while receiving the usual dose of betaine raised concern. However this issue was adequately dealt with in the SPC and the provided RMP.

User consultation

Results of assessments carried out in cooperation with target patient groups on the package leaflet ('User Consultation' of the package leaflet according to (Art 59(3) and 61(1) of the amended Directive) were presented. Data included the method, background information and results of the testing procedures.

The proposed product information submitted was considered satisfactory as the leaflet tested accounted for the changes as requested in the Day 120 LOQ for the product and as such additional testing was not considered necessary.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Apart registry no additional pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed.
- no additional risk minimisation activities were required beyond those included in the product information.

Betaine was shown to be useful as an adjunctive therapy to the existing treatment of homocystinuria. It is no substitute for other currently available therapies such vitamin supplementation or dietary intervention. When used as indicated, betaine seems to have a favourable benefit to risk ratio. Although there were only a few systematic studies available, data presented in this application showed both biochemical and clinical benefits of betaine supplementation in the management of homocystinuria and that Cystadane has a positive risk-benefit ratio in the treatment of these patients.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Cystadane in the adjunctive treatment of homocystinuria was favourable and therefore recommended the granting of the marketing authorisation.

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 50 mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 147.24 mg of cysteamine bitartrate (mercaptamine bitartrate, INN), corresponding to 50 mg of cysteamine free base.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Hard Capsule

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).

The drug is best tolerated if 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 at a temperature appropriate for eating. 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 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 Contra-indications

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 Pregnancy and lactation and section 5.3 Preclinical safety data), as it is teratogenic in animals.

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

4.4 Special warnings and special precautions for use

Special warnings:
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).

A few cases of molluscoid pseudotumor on elbows have been reported in children treated with high doses of cysteamine. These skin lesions were associated with skin striae and bone lesions first seen during an X-ray examination.
It is therefore recommended to monitor skin and bones with regular physical and X-ray examinations. 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.

CYSTAGON should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (see section 4.6 Pregnancy and lactation and section 5.3 Preclinical safety data), as it is teratogenic in animals.

Special precautions for use:
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 Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of interaction

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 medications have been used with cysteamine.

4.6 Pregnancy and lactation

See 4.3. Contraindications

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 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 lactating mothers and neonates (see 5.3), breast-feeding is contra-indicated in women taking CYSTAGON.

4.7 Effects on 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 drug 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 (> 10%), common (1-10%) and uncommon (0.1-1%).

Blood and lymphatic system disorders	*Uncommon*: Leukopenia
Immune system disorders	*Uncommon*: Anaphylactic reaction
Metabolism and nutrition disorders	*Very common*: Anorexia
Psychiatric disorders	*Uncommon*: Nervousness, hallucination
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
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.

Renal and urinary disorders	*Uncommon*: Nephrotic syndrome
General disorders and administration site conditions	*Very common*: Lethargy, pyrexia *Common*: Asthenia
Investigations	*Common*: Liver function tests abnormal

Two cases of nephrotic syndrome have been reported within 6 months of starting therapy with progressive recovery after treatment discontinuation. Histology showed a membranous glomerulonephritis of the renal allograft in one case and hypersensitivity interstitial nephritis in the other.

A few cases of molluscoid pseudotumor on elbows have been reported in children treated chronically with high doses of cysteamine (at least 2.5 g/m^2/day).
In some cases, these skin lesions were associated with skin striae and bone lesions first seen during an X-ray examination. Bone lesions reported were osteopenia, compression fractures, scoliosis and genu valgum along with leg pain and hyperextensive joints.
One patient subsequently died of acute cerebral ischemia with marked vasculopathy.
In most of 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).

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, 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 ($\pm$ sd) value: 1.8 ± 0.8 hours) slightly later than the peak plasma cysteamine concentration (mean ($\pm$ 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 beetwen 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

Microcrystalline cellulose, pregelatinized starch, magnesium stearate/sodium lauryl sulfate, colloidal silicon dioxide, croscarmellose sodium, gelatin, titanium dioxide, black ink on hard capsules (E172, E132, E129, E133, E104).

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 white, opaque hard capsules with CYSTA 50 on the body and MYLAN on the cap. 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 Instructions for use and handling

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 at a temperature appropriate for eating. 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.

7. MARKETING AUTHORISATION HOLDER

Orphan Europe SARL
Immeuble "Le Guillaumet"
F-92046 Paris La Défense
France

8. NUMBERS IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

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 renewal of the authorisation: 23 June 2002.

10. DATE OF REVISION OF THE TEXT

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orphan Europe SARL, Immeuble "Le Guillaumet", F-92046 Paris La Défense, France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual re-assessment of the benefit/risk profile.

The company should continue to provide a report on the clinical information obtained by using the agreed revised clinical record forms on a yearly basis in view of the annual re-assessment.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON CYSTAGON 50 mg x 100 hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CYSTAGON 50 mg Hard Capsules
Cysteamine bitartrate (mercaptamine bitartrate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule of CYSTAGON 50 mg contains 147.24 mg of cysteamine bitartrate (mercaptamine bitartrate) corresponding to 50 mg of cysteamine free base

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

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

Orphan Europe SARL
Immeuble "Le Guillaumet"
F-92046 Paris La Défense
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/039/001

13. MANUFACTURER'S BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PACKAGE LEAFLET
CYSTAGON 50 mg Hard Capsules

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

CYSTAGON 50 mg Hard Capsules
Cysteamine bitartrate (mercaptamine bitartrate)

- The active substance is cysteamine bitartrate (mercaptamine bitartrate). Each hard capsule of CYSTAGON 50 mg contains 147.24 mg of cysteamine bitartrate (mercaptamine bitartrate), corresponding to 50 mg of cysteamine free base.
- The other ingredients are microcrystalline cellulose, starch, pregelatinized, magnesium stearate/sodium lauryl sulphate, colloidal silicon dioxide, croscarmellose sodium, gelatin, titanium dioxide, black ink on hard capsules (E172, E132, E129, E133, E104).

Marketing authorisation holder and Manufacturer
Orphan Europe SARL
Immeuble "Le Guillaumet"
F-92046 Paris La Défense
France

1. WHAT CYSTAGON IS AND WHAT IT IS USED FOR

CYSTAGON 50 mg Hard Capsules is presented in bottles of 100 and 500 hard capsules with a desiccant in the bottle.

CYSTAGON is prescribed to manage nephropathic cystinosis, a rare inherited disorder characterized by the build up of cystine in some organs, such as kidneys. Cystine build up causes kidney damage and excretion of excess amounts of glucose, proteins and electrolytes. CYSTAGON is a medication that reacts with cystine to decrease its level in cells.

2. BEFORE YOU USE CYSTAGON

Do not use CYSTAGON :
- if you or your child has developed hypersensitivity (allergy) to it or to cysteamine or penicillamine.
- if you are breast-feeding.

You should not use CYSTAGON if you are pregnant.

Take special care with CYSTAGON :

- This medicine has been prescribed for you or your child only.
  Do not give this drug to others who may have similar symptoms. Do not use it for any other reason.
- A few cases of skin lesions on elbows like little hard lumps have been reported in children treated with high doses of cysteamine. These lesions were associated with skin striae and bone lesions such as fracture and bone deformities, and with laxity of joints.
  Your or your child's doctor could arrange for regular physical and X-ray examination to be done. Self examination of your or your child's skin is recommended. If any skin or bone abnormalities appear, please inform your doctor immediately.
- 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, CYSTAGON does not contain phosphate. You may already be receiving phosphate supplements and the dose of these may need to be altered when CYSTAGON is substituted for phosphocysteamine.

Using 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 should 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.

Using other medicines :
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE CYSTAGON

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.

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 or persistent vomiting occurs.

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 double the dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CYSTAGON can have side effects.

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

The following side effects were reported:
- Very common (>10%): vomiting, nausea, diarrhoea, loss of appetite, fever and lethargy.
- Common (1-10%): abdominal pain or discomfort, unpleasant breath and body odour, skin eruption, gastroenteritis, asthenia, headache, encephalopathy and liver function test abnormalities.
- Uncommon (0.1-1%): skin striae, skin lesion (little-hard lumps on elbows), joint laxity, leg pain, bone fracture, scoliosis, bone deformity and fragility, hair discoloration, 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.

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING CYSTAGON

Keep out of the reach and sight of children.

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

Do not use after the expiry date stated on the packaging.

If you see any signs of deterioration in a bottle of capsules, take the bottle back to your pharmacist.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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