AUSTRALIAN PRODUCT INFORMATION

CYSTAGON®

(mercaptamine (cysteamine) (as bitartrate)) capsule

1 NAME OF THE MEDICINE

Mercaptamine (cysteamine) bitartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CYSTAGON capsule contains either 50 mg or 150 mg of mercaptamine free base as mercaptamine bitartrate.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

CYSTAGON capsules for oral administration, contain mercaptamine bitartrate, a cystine depleting agent which lowers the cystine content of cells in patients with cystinosis, an inherited defect of lysosomal transport.

CYSTAGON 50 mg are white, opaque capsules printed with CYSTA 50 on the body and MYLAN on the cap.

CYSTAGON 150 mg are white, opaque capsules printed with CYSTAGON 150 on the body and MYLAN on the cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CYSTAGON is indicated for the management of nephropathic cystinosis in children and adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

The initial dose is 0.2 to 0.3 g/m^2/day, given in four divided doses, increasing over 4 to 6 weeks to a maintenance dose of 1.3 g/m^2/day given in four divided doses for children up to 12 years. The maintenance dose of 1.3 g/m^2/day can be calculated from the following table which is based on weight and surface area.

Weight in kg	**mg of mercaptamine Free Base Every 6 hours**
0 – 2	100
2.5 – 5	150
5 – 6.5	200
6.5 – 9	250
9 – 10.5	300
10.5 – 14.5	350
14.5 – 19	400
19 – 23	450
> 23	500

Patients over 12 years old and 50 kg body weight should receive 2 g/day in four divided doses. This dose should be reached after 4 to 6 weeks as stated above.

If the patient cannot tolerate a specific dose, therapy should be stopped temporarily and restarted at a lower dose.

Intact capsules should not be administered to children under the age of approximately 6 years due to the risk of aspiration. The contents of the capsules may be sprinkled over food for children of this age.

Leukocyte Cystine Concentration

The aim of therapy is to keep the leukocyte cystine concentration below 1 nmol of half-cystine/mg protein, 5 to 6 hours after administration of CYSTAGON. Patients unable to tolerate the recommended dose will still benefit if the leukocyte concentrations are below 2 nmol of half-cystine/mg protein. A maximum dose of 1.95 g/m^2/day may be considered to achieve a concentration below 1 nmol of half-cysteine/mg protein if this dose can be tolerated.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If a skin rash develops, CYSTAGON should be withheld until the rash clears. CYSTAGON may be restarted at a lower dose under close supervision, then slowly titrated to the therapeutic dose. If a severe skin rash develops such as erythema multiforme bullosa or toxic epidermal necrolysis, CYSTAGON should not be readministered.

CNS symptoms such as seizures, lethargy, somnolence, depression, and encephalopathy have been associated with mercaptamine. If CNS symptoms develop, the patient should be carefully evaluated, and the dose adjusted as necessary. Neurological complications have been described in some cystinotic patients not on mercaptamine treatment. This may be a manifestation of the primary disorder. Patients should not engage in hazardous activities until the effects of CYSTAGON on mental performance are known.

Gastrointestinal tract symptoms including nausea, vomiting, anorexia, and abdominal pain have been associated with mercaptamine, sometimes severe. In addition, gastrointestinal ulceration and bleeding have been reported in patients on mercaptamine bitartrate therapy. Physicians should remain alert for signs of ulceration and bleeding and should inform patients and/or parents or guardians about the signs and symptoms of serous GI toxicity and what steps to take if they occur. If these develop, therapy may have to be interrupted and the dose adjusted. A mercaptamine dose of 1.95 g/m^2/day (approximately 80 to 90 mg/kg/day) was associated with an increased number of withdrawals from treatment due to intolerance and an increased incidence of adverse events.

Post-marketing reports include one report of interstitial nephritis with early renal failure. A causal relationship between this event and mercaptamine bitartrate therapy has not been established.

There have been post-marketing reports of serious skin lesions in patients treated with high doses of CYSTAGON or other mercaptamine salts that have responded to mercaptamine dose reduction. These skin lesions are purplish haemorrhagic lesions over the elbow area on both arms and have been described as molluscoid pseudotumors. Skin striae, bone lesions (that have been described as osteopenia, compression fractures, scoliosis and genu valgum) along with leg pain and joint hyperextension may also be present. One patient with serious skin lesions subsequently died of acute cerebral ischemia with marked vasculopathy. Physicians should routinely monitor the skin and bones of patients receiving CYSTAGON. If similar skin or bone abnormalities appear, the dose of CYSTAGON should be reduced.

There have been post-marketing reports of benign intracranial hypertension (or pseudotumor cerebri; PTC) and/or papilledema associated with CYSTAGON treatment that has resolved with the addition of diuretic therapy. PTC may be more common in cystinotic patients because of concurrent medication and renal transplantation. Although a causal relationship of PTC to CYSTAGON has not been established, physicians should monitor patients receiving CYSTAGON for this condition. Physicians should instruct patients to report any of the following symptoms: headache, tinnitus, dizziness, nausea, diplopia, blurry vision, loss of vision,

pain behind the eye or pain with eye movement. A periodic eye examination is needed to identify this condition early and timely treatment should be provided when it occurs to prevent vision loss.

Mercaptamine has occasionally been associated with reversible leukopenia and abnormal liver function studies. Therefore, blood counts and liver function studies should be monitored.

Use in the Elderly

No data available.

Paediatric Use

The safety and effectiveness of CYSTAGON for cystinotic children have been established. Mercaptamine therapy should be initiated as soon as the diagnosis of nephropathic cystinosis has been confirmed.

Take adequate precautions during use in children at risk of aspiration. There is a risk of suffocation due to aspiration.

Use in Neonates

Cataract formation was seen in neonatal rats dosed with mercaptamine hydrochloride for the first six days of life. However, delayed exposure of neonatal rats to mercaptamine (treatment day 10 through 16) resulted in the absence of cataract formation.

Based on the results of these studies, human neonates dosed with CYSTAGON should be monitored for the possibility of cataract formation.

Effects on Laboratory Tests

Leukocyte cystine measurements are useful to determine adequate dosage and compliance. When measured 5 to 6 hours after CYSTAGON administration, the goal should be a level < 1 nmol of half-cystine/mg protein. In some patients with poorer tolerability for CYSTAGON, patients may still receive benefit with a white cell cystine level of less than 2 nmol of half-cystein/mg protein. Measurements should be done every three months, more frequently when patients are transferred from mercaptamine hydrochloride or phosphocysteamine solutions to CYSTAGON.

Physicians should follow patients for signs and symptoms of gastrointestinal ulcerations and bleeding and should inform patients and/or guardians of the importance of this follow-up.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

None had been described.

CYSTAGON can be administered with electrolyte and mineral replacements necessary for management of the Fanconi Syndrome as well as vitamin D and thyroid hormone.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproduction studies were conducted in male and female rats. Mercaptamine reduced the fertility of adult rats at an oral dose of 375 mg/kg/day (1.5 times the maximum recommended human dose, based on body surface area). There was no effect on fertility and reproductive performance at an oral dose of 75 mg/kg/day (0.2 times the maximum recommended human dose, based on body surface area).

Use in Pregnancy

Pregnancy Category: B3

There are no adequate and well controlled studies in pregnant women. Teratology studies have been performed in the rat at oral doses in a range of 37.5 to 150 mg/kg/day (about 0.2 to 0.7 times the recommended human maintenance dose on a body surface basis) and have revealed mercaptamine bitartrate to be teratogenic and fetotoxic. Observed teratogenic findings were cleft palate, Kyphosis, heart ventricular septal defects, microcephaly and exencephaly.

CYSTAGON should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

It is not known whether mercaptamine is excreted in human milk. Mercaptamine reduced the survival of the offspring of adult rats dosed orally with 375 mg/kg/day (1.5 times the maximum recommended human dose based on body surface area).

CYSTAGON should be used during breastfeeding only if the potential benefit justifies the potential risk to the foetus.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In three clinical trials, mercaptamine or phosphomercaptamine have been administered to 246 children with cystinosis. Causality or side effects are sometimes difficult to determine because adverse effects may result from the underlying disease.

The most frequent adverse reactions seen involve the gastrointestinal and central nervous systems. These are especially prominent at the initiation of mercaptamine therapy. Temporarily suspending treatment, then gradual reintroduction, may be effective in improving tolerance.

Adverse reactions were not collected systemically in the NCCS; but were often listed by investigators. The following rates may therefore be underestimated. The most common events were vomiting, anorexia, fever, diarrhoea, lethargy and rash.

The common (> 1%) and uncommon (0.1 – 1%) adverse events for CYSTAGON were:

Body as a whole:

Common: Fever (22%), lethargy (11%)

Uncommon: Dehydration

Cardiovascular:

Uncommon: Hypertension

Digestive:

Common: Diarrhoea (16%), vomiting (35%)

Uncommon: Nausea, bad breath, abdominal pain, dyspepsia, constipation, gastroenteritis, duodenitis, gastrointestinal ulceration, bleeding

Metabolic and nutritional:

Common: Anorexia (31%)

Central nervous system:

Uncommon: Somnolence, encephalopathy, headache, seizures, ataxia, confusion, tremor, hyperkinesia, decreasing hearing, dizziness, jitteriness

Skin:

Common: Rash (7%)

Psychiatric:

Uncommon: Nervousness, abnormal thinking, depression, emotional lability, hallucinations, nightmares

Integumentary:

Uncommon: Urticaria

Urogenital:

Uncommon: Interstitial nephritis, renal failure (see section 4.4 Special Warnings and Precautions for Use)

Clinical laboratory:

Uncommon: Abnormal liver function, anaemia, leukopenia

Adverse reactions or intolerance leading to cessation of treatment occurred in 8% of patients in the US studies.

Withdrawals due to intolerance, vomiting associated with medication, anorexia, lethargy and fever appeared dose-related, occurring more frequently in those patients receiving 1.95 g/m^2/day as compared to 1.30 g/m^2/day.

	Dose in g/m^2/day	
	1.30 (n = 42) %	**1.95 (n = 51) %**
Vomiting considered related to medicine	31	67
Anorexia	33	51
Lethargy	17	27
Diarrhoea	31	31
Fever	28	45

Sudden deaths have been reported in this disease state.

General disorders:

Uncommon: Lethargy, pyrexia

Post-marketing Surveillance

Benign intracranial hypertension (or pseudotumour cerebri; PTC) with papilledema; skin lesions, molluscoid pseudotumours, skin striae, skin fragility; joint hyperextension, leg pain, genu valgum, osteopenia, compression fracture and scoliosis have been reported (see section 4.4 Special Warnings and Precautions for Use). In addition, non-serious hair colour changes have been reported.

Drug abuse and dependence

CYSTAGON has not been associated with abuse potential, psychological or physical dependence in humans.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/safety/reporting-problems.

4.9 OVERDOSE

Overdoses of up to 250 mg/kg have been reported. Symptoms of overdose include vomiting, dehydration, progressive lethargy and cardiac arrest. There is no specific antidote. Respiratory and cardiovascular support may be required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Normal individuals and persons heterozygous for cystinosis have white cell cystine levels of < 0.2 and usually below 1nmol of half-cystine/mg protein, respectively. Individuals with nephropathic cystinosis have elevations of white cell cystine above 2 nmol of half-cystine/mg protein. White cell cystine is monitored in these patients to determine adequacy of dosing, levels being measured 5 to 6 hours after dosing. In the Long-Term Study (see section 5.1 Pharmacodynamic Properties – Clinical Trials) entry white cell cystine levels were 3.73 nmol of half-cystine/mg protein (range 0.13 to 19.80 nmol of half-cystine/mg protein) and were maintained close to 1 nmol of half-cystine/ mg protein with a mercaptamine dose range of 1.3 to 1.95 g/m^2/day. After administration of mercaptamine HCl, leukocyte cystine levels fall, with minimum levels at approximately 1 hour.

Because mercaptamine HCl has an unpleasant taste and odour, other formulations have been developed, including phosphocysteamine, the phosphorothioester of mercaptamine that is rapidly converted to mercaptamine in the gut, and mercaptamine bitartrate. Mercaptamine bitartrate has been shown in a transfer study in 8 patients to maintain white cell cystine levels below 1 nmol of half-cystine/mg protein when substituted for mercaptamine HCl or phosphocysteamine. Total mercaptamine levels 2- and 6-hours post-dosing were higher after mercaptamine bitartrate than for the solutions. Most clinical data have been developed using mercaptamine HCl or phosphocysteamine solutions. In all discussions that follow, administered amounts of various mercaptamine salts will be expressed as amounts of mercaptamine free base.

Mechanism of Action

Cystinosis is an autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal; in the nephropathic form, accumulation of cystine and formation of crystals damage various organs, especially the kidney, leading to renal tubular Fanconi Syndrome and progressive glomerular failure, with end stage renal failure by the end of the first decade of life. In four studies of cystinosis patients before mercaptamine was available, renal death (need for transplant or dialysis) occurred at a median age of less than 10 years. Patients with cystinosis also experience growth failure, rickets and photophobia due to cystine deposits in the cornea. With time, most organs are damaged, including the retina, muscles and central nervous system.

Mercaptamine is an aminothiol that participates within lysosomes in a thiol-disulfide interchange reaction converting cystine into cysteine and cysteine-mercaptamine mixed disulphide, both of which can exit the lysosome in patients with cystinosis.

Clinical Trials

There are approximately 200 pre-transplant cystinosis patients in the United States with nephropathic cystinosis and clinical studies have included almost all of them, in addition to about 40 studied in the United Kingdom. For all patients, mean age of entry into studies was just under 4 years. Patients were approximately equally divided between genders and about 85% were white, 9% were black and 3% were Hispanic.

The National Collaborative Cysteamine Study (NCCS) treated 94 children (mainly from the United States) with nephropathic cystinosis with increasing doses of mercaptamine HCl (mean dose 54 mg/kg/day) to attain white cell cystine levels of less than 2 nmol of half-cystine/mg protein 5 to 6 hours post-dose, and compared their outcome with an historical control group of 17 children who had been in the placebo group of a randomised placebo-controlled trial of ascorbic acid. Mercaptamine treated patients had been diagnosed at a mean age of 22 months and were a mean age of 46 months old at study entry; placebo patients had been diagnosed at about 29 months and were a mean age of about 52 months old at study entry. The principal measures of effectiveness were serum creatinine and calculated creatinine clearance and growth (height).

The average median white cell cystine level attained during treatment in the NCCS was 1.7 ± 0.2 nmol of half-cystine/mg protein. There were 70 mercaptamine patients with baseline serum creatinine less than 2 mg/dL who were followed for at least a year and 17 placebo patients. Twelve of the 94 mercaptamine treated patients required early dialysis or renal transplant. Median follow-up of mercaptamine patients was over 32 months and 20% were followed more than 5 years. For the placebo group, median follow-up was 20 months and only one was followed more than 24 months. Among mercaptamine patients, glomerular function was maintained over time despite the longer period of treatment and follow-up. Placebo treated patients, in contrast, experienced a gradual rise in serum creatine. Height, corrected for age, was compared for treated patients with the height, at the various age's patients appeared, of the 143 patients initially screened for inclusion in the NCCS. Patients on treatment maintained growth (did not show increasing growth failure compared to normal) although growth velocity did not increase enough to allow patients to catch up to age norms. Renal tubular function was not affected by treatment.

The Long-Term Study, initiated in 1988, utilised both mercaptamine HCl and phosphomercaptamine (patient's choice) in 46 patients who had completed the NCCS (averaging 6.5 years of treatment) and 93 new patients. Patients had cystinosis diagnosed by elevated white cell cystine (mean 3.63 nmol of half- cystine/mg). New patients and 46 continuing patients were required to have serum creatinine less than 3.0 mg/dL and 4.0 mg/dL, respectively. Patients were randomised to doses of 1.3 or 1.95 g/m^2/day and stratified according to whether the serum creatinine was above 1.2 mg/dL or not. Doses could be raised if white cell cystine levels were approximately 2 nmol of half- cystine/mg protein and lowered due to intolerance.

Mean doses were 1.27 g/m^2/ day and 1.87 g/m^2/day in the two groups and white cell cystine levels averaged 1.72 ± 1.65 nmol of half- cystine/mg protein and 1.86 ± 0.92 nmol of half- cystine/mg protein in the 1.3 and 1.95 g/m^2/day groups, respectively. In new patients, a group similar in age to the NCCS group, serum creatinine was essentially unchanged over the period of follow-up (about half of the patients were followed for 24 months) and phosphomercaptamine and mercaptamine HCl had similar effects. The long-term follow-up group, about nine years old on average at entry, stayed in the study (almost 80% were followed at least 2-years) and had essentially no change in renal function. In four studies of untreated cystinosis, renal death (need for transplant or dialysis) occurred at median age of less than 10 years. Both groups maintained height (although they did not catch up from baseline). There was no apparent difference between the two doses.

5.2 PHARMACOKINETIC PROPERTIES

Absorption, Distribution, Metabolism, Excretion

Eleven children aged 3 - 14 years with nephropathic cystinosis and established on CYSTAGON capsules for at least 12 months were given their regularly scheduled dose of 8 - 16 mg/kg and then pharmacokinetic parameters measured. Mercaptamine from the capsules was rapidly absorbed (mean ± se time to maximum serum concentration, 1.4 ± 0.1 hours), distributed extensively to tissues (mean ± se volume of distribution, 150 ± 20 L) and rapidly cleared (mean ± se, 1140 ± 130 mL/min). The mean elimination half-life was 1.5 hours. The rise in serum mercaptamine concentration correlated with a fall in leukocyte cystine concentration. Mean ± se time to trough leukocyte cystine concentration was 1.8 ± 0.2 hours.

Special Considerations

There are special problems encountered in studying adequate numbers of patients with a disease state as rare as nephropathic cystinosis. Owing to the limited number of patients and the deficiencies associated with

clinical studies of such rare disease states, caution should be taking in interpreting the clinical data on the use of this drug.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mercaptamine showed no evidence of mutagenic potential in assays for gene mutations (bacteria). In assays of chromosomal damage and interactions with DNA, mercaptamine was clastogenic (rat liver cells and human lymphocytes in vitro) and caused sister chromatid exchanges in vitro (Chinese hamster cells but not human lymphocytes).

Mercaptamine was negative in a mouse micronucleus test.

Carcinogenicity

Mercaptamine has not been tested for carcinogenic potential in long-term animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CYSTAGON capsules contain the following inactive ingredients: microcrystalline cellulose, pregelatinized maize starch, magnesium stearate, sodium lauryl sulfate, silicon dioxide, croscarmellose sodium, titanium dioxide and gelatin.

The printing inks contain Shellac, ethanol, iron oxide black, butan-1-ol, propylene glycol, isopropyl alcohol, sulfuric acid and strong ammonia solution.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules are supplied in a HDPE bottle in a pack size of 500.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 60451 - CYSTAGON mercaptamine (cysteamine) (as bitartrate) 50mg capsule bottle

AUST R 60452 - CYSTAGON mercaptamine (cysteamine) (as bitartrate) 150mg capsule bottle

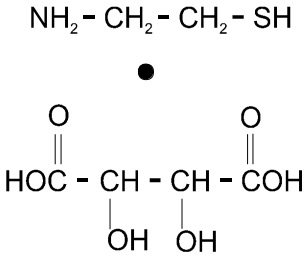
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

CYSTAGON is the bitartrate salt of mercaptamine, an aminothiol, beta-mercaptoethylamine. Mercaptamine bitartrate is a highly water soluble white powder.



Chemical name: Ethanethiol, 2-amino, [R-(R*,R*)]2,3-dihydroxybutanedioate (1:1) (salt) (9CI)

Molecular formula: $C_2H_7NS.C_4H_6O_6$

Molecular weight: 227

CAS Number

27761-19-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

5/08/1997

10 DATE OF REVISION

23/01/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes

CYSTAGON® is a Viatris company trade mark

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