1. NAME OF THE MEDICINAL PRODUCT

Cystadrops 3.8 mg/ml

eye drops solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains mercaptamine hydrochloride equivalent to 3.8 mg mercaptamine (cysteamine).

Excipient with known effect:
Each mL of eye drops solution contains 0.1 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops solution.

Viscous, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cystadrops is indicated for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis.

4.2 Posology and method of administration

Treatment with Cystadrops should be initiated under the supervision of a physician experienced in the management of cystinosis.

Posology

The recommended dose is one drop in each eye, 4 times a day during waking hours. The recommended interval between each instillation is 4 hours. The dose could be decreased progressively (to a minimum total daily dose of 1 drop in each eye) depending on the results of ophthalmic examination (such as, corneal cystine crystal deposits, photophobia).
If the patient misses an instillation, the patient should be told to continue the treatment with the next instillation.
The dose should not exceed 4 drops a day in each eye.
The accumulation of corneal cystine crystals increases if Cystadrops is discontinued. The treatment should not be stopped.

Paediatric population
Cystadrops may be used in paediatric patients from 2 years of age at the same dose as in adults (see section 5.1).
The safety and efficacy of Cystadrops in children aged less than 2 years has not been established. No data are available.

Method of administration

For ocular use.

Before the first admnistration, in order to facilitate the administration, the patient should be told to bring back Cystadrops at room temperature. After first opening, the patient should be told to keep the dropper bottle at room temperature.

To avoid sticky eyes in the morning, the patient should be advised to apply the last drop of the day at least 30 minutes before going to bed.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the dropper bottle.

The patient should be told to discard the dropper bottle after 7 days of use.

In case of concomitant therapy with other topical ocular medicinal products, an interval of ten minutes should be allowed between successive applications. Eye ointments should be administered last.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Cystadrops contains benzalkonium chloride which may cause eye irritation.

Benzalkonium chloride, which is commonly used as a preservative in ophtalmic products, has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Monitoring is required.

Contact lenses
Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients should be instructed to remove contact lenses prior to the administration of the eye drops and wait at least 15 minutes before re-inserting contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Since the recommended total daily dose of cysteamine base is no more than approximately 0.4% of the highest recommended oral dose of cysteamine base in any age group, no interactions with orally administered medicinal products are anticipated.

4.6 Fertility, pregnancy and lactation

The recommended total daily ocular dose of cysteamine is no more than approximately 0.4% of the highest recommended dose of oral cysteamine in any age group. Systemic exposure of cysteamine following ocular administration is therefore lower than following oral administration. Although no effects during pregnancy and breast-feeding are anticipated, since systemic exposure to cysteamine is negligible, precautions should be taken with concomitant treatment with oral cysteamine.

Pregnancy
There are no adequate data from the use of cysteamine 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, oral cysteamine 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
Cysteamine 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), women taking oral cysteamine should not breast-feed.

Fertility
No data on the effect of cysteamine on human fertility are available. Studies in animals have shown a reduction on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Cystadrops may have a minor influence on the ability to drive and use machines.
Temporary (in average less than 1 minute) blurred vision or other visual disturbances may affect the ability to drive or use machines.
If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are eye pain, ocular hyperaemia, eye pruritus, lacrimation increased, blurred vision or eye irritation. The majority of these adverse reactions are transient and most are mild or moderate.

Tabulated list of adverse reactions
The following adverse reactions were reported during clinical trials and the French NPU programme with Cystadrops. Reported adverse reactions are listed below, by system organ class and by frequency (by patient).
Frequencies are defined as*:* very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	**Adverse reactions**
Eye disorders	Very common : eye pain, vision blurred, eye irritation, ocular hyperaemia, eye pruritus, lacrimation increased, deposit eye Common : abnormal sensation in eye, dry eye, foreign body sensation in eye, eyelid oedema, eyelid irritation, visual impairment, hordeolum
General disorders and administration site conditions	Very common : instillation site discomfort (mainly sticky eyes and sticky eyelashes) Common : instillation site pain

Paediatric population
Frequency, type and severity of adverse reactions in children are the same as in adults.
69 paediatric patients were followed through clinical trials and the French NPU programme. 19 patients were under 6 years old, 21 between 6 and 12 years old and 29 between 12 and 18 years old.

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

Overdose is unlikely to occur with ocular administration.

In case of accidental ingestion, monitoring and symptomatic management of the patient should be implemented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophtalmologicals, other ophtalmologicals, ATC code: S01XA21.

Mechanism of action
Cysteamine reduces corneal cystine crystal accumulation acting as a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides.

Clinical efficacy and safety
Two clinical trials were performed with Cystadrops: a single arm clinical trial on 8 children and adults (OCT-1 study) and a randomised, multi-centre, open label, active controlled phase III clinical trial (CHOC study) conducted on 32 patients.

OCT-1 study
This study assessed the safety and efficacy of Cystadrops during 5 years. Dose adaptation was performed following ocular examination. None of the patients discontinued treatment over the 5 year follow-up.
The efficacy was assessed with In-Vivo Confocal Microscopy total score (IVCM score) by quantifying the cystine crystals in the 7 layers of the cornea. After 30 days of treatment and at a median frequency of 4 instillations per day, an average 30% decrease in the IVCM total score was observed. A mean decrease in corneal cystine crystal deposits of 30%, in comparison with baseline, was maintained over time with a median dosing regimen of 3 drops/eye/day (range 1-3 drops) for 7 of the 8 patients. Photophobia tended to improve over time.

CHOC study
This study was a randomised, controlled trial to assess the efficacy and the safety profile of Cystadrops following a period of 90 days of treatment at a dose regimen of 4 drops/eye/day. The IVCM total score was the primary efficacy endpoint. 15 patients were exposed to Cystadrops. The mean IVCM total score was calculated for 11 patients. A trend towards a lower IVCM total score in Cystadrops arm was observed at day 30. The mean decrease by 40% in the Cystadrops arm was confirmed at day 90. Superiority of Cystadrops was demonstrated compared to the control arm (cysteamine hydrochloride 0.10%) $p<0.001$ 95% CI (2.11; 5.58). Superiority of Cystadrops was also demonstrated for photophobia rated by the investigator compared to the control arm (cysteamine hydrochloride 0.10%) $p< 0.048$ 95% CI (0.23; 1.14).

Paediatric population
Clinical data on safety and efficacy were collected during the 2 clinical trials (OCT-1 and CHOC studies). In total 15 paediatric patients were exposed to Cystadrops whereof 3 subjects (including one 2 year and one 3 year old subject) being less than 6 years of age. The efficacy and safety results are similar in both paediatric and adult populations.

5.2 Pharmacokinetic properties

Human pharmacokinetic assessment following ocular administration of Cystadrops was not performed.

Similarly to other topically administered ocular products, systemic absorption is likely to occur. However it should be considered that the recommended daily dose of cysteamine applied as eye drops is no more than approximately 0.4% of the highest recommended daily oral dose of cysteamine in any age group.

5.3 Preclinical safety data

Systemic exposure following ocular administration is anticipated to be low. When there is concomitant use of ocular and oral treatment with cysteamine the contribution to any systemic risk from ocular administration is considered negligible.

Preclinical data on oral cysteamine:
Genotoxicity studies have been performed: induction of chromosome aberrations in cultured eukaryotic cell lines has been reported and specific studies with cysteamine 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 cysteamine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 1M
Carmellose sodium (Blanose 12M31P)
Citric acid monohydrate
Sodium hydroxide
Disodium edetate
Benzalkonium chloride 50% solution
Sodium hydroxide 1M
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

After first opening: 7 days. Store below 25°C. Do not refrigerate. Keep the dropper bottle tightly closed in the outer carton in order to protect from light.

6.4 Special precautions for storage

Before first opening:
Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

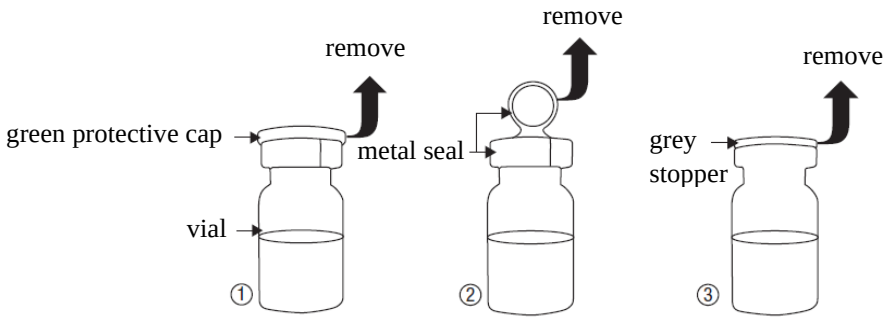
5 mL solution in a 10 mL amber glass vial closed by a bromobutyl stopper and sealed with an aluminium tear-off cap. A PVC dropper applicator with HDPE closure is packed separately and included in each carton box.

Each carton box contains 1 vial and 1 dropper applicator.

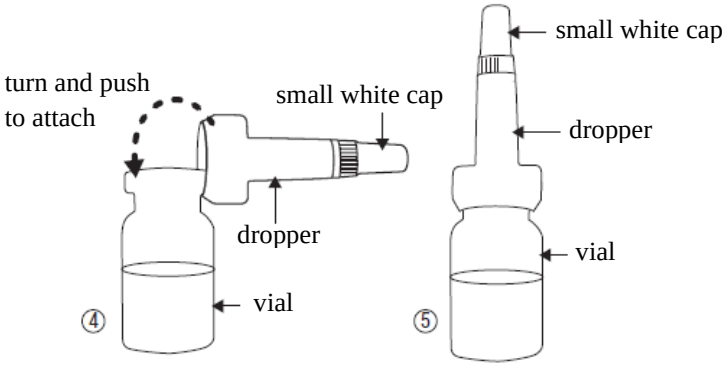
6.6 Special precautions for disposal and other handling

The patient should be advised to follow the instructions below for opening of the vial and attachement of the dropper applicator:

- Wash your hands carefully in order to avoid microbiological contamination of the content in the vial.
- Remove the green protective cap (picture 1).
- Remove the metal seal (picture 2).
- Remove the grey stopper (picture 3) from the vial.
- Do not touch the opening of the vial after removing the grey stopper.



- Take the dropper out of its sachet, without touching the end intended to be attached to the vial, attach it (picture 4) to the vial and do not remove it.



- Make sure that you do not lose the small white cap (picture 5) that comes on the top of the dropper.

7. MANUFACTURER

Recordati Rare Diseases
Immeuble “Le Wilson”
70, Avenue du Général de Gaulle
92800 Puteaux
France

8. LICENSE HOLDER

Medison Pharma Ltd., 10 Hashiloach St., P.O.B 7090, Petach Tikva

Registration Number 164-69-35476

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