

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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 administration, 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

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.

Excipients with known effect

Cystadrops contains benzalkonium chloride which may cause eye irritation.

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

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$), not known (cannot be estimated from the available data).

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

professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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: Ophthalmologicals, other ophthalmologicals, 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%) $p < 0.0001$ 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%) $p = 0.0048$ 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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Cystadrops in one or more subsets of the paediatric population in the treatment of corneal cystine crystal deposits in cystinosis patients (see section 4.2 for information on paediatric use).

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 embryofetotoxic 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/m²/day in the rat, which is less than half the recommended clinical maintenance dose of cysteamine, i.e. 1.30 g/m²/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 medicinal product 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 medicinal product causes depletion of somatostatin in several animal species. The consequence of this for the clinical use of the medicinal product is unknown.

No carcinogenic studies have been conducted with cysteamine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Carmellose sodium
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)
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

6 months

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.

Pack of 1 carton box or multipack containing 4 carton boxes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

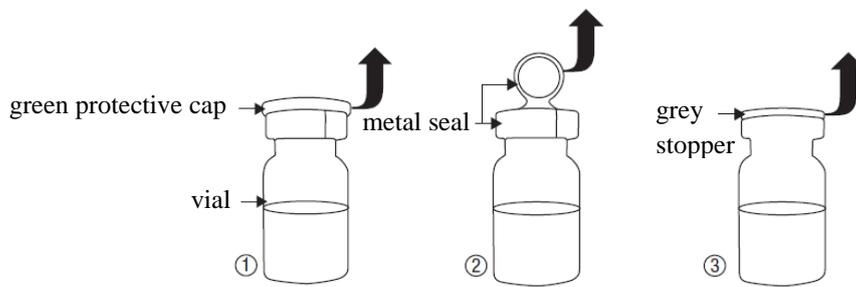
The patient should be advised to follow the instructions below for opening of the vial and attachment of the dropper applicator:

- 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.

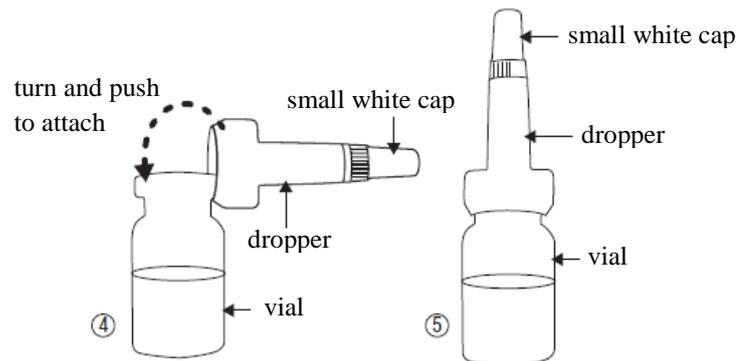
remove

remove

remove



- 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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1049/001
 EU/1/15/1049/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2017
 Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Recordati Rare Diseases
Immeuble "Le Wilson"
70, avenue du Général de Gaulle
FR-92800 Puteaux
France

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports (PSURs)

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Cystadrops 3.8 mg/mL eye drops solution
cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 3.8 mg of cysteamine (mercaptamine), as hydrochloride.

3. LIST OF EXCIPIENTS

Excipients: benzalkonium chloride (see leaflet for further information), disodium edetate, carmellose sodium, citric acid monohydrate, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops solution

1 vial of 5 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard 7 days after first opening.
Opened on:

9. SPECIAL STORAGE CONDITIONS

Before first opening: store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble "Le Wilson"
70 Avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1049/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystadrops

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Cystadrops 3.8 mg/mL eye drops solution
cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 3.8 mg of cysteamine (mercaptamine), as hydrochloride.

3. LIST OF EXCIPIENTS

Excipients: benzalkonium chloride (see leaflet for further information), disodium edetate, carmellose sodium, citric acid monohydrate, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops solution

Multipack: 4 (4 packs of 1) vials of 5 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard 7 days after first opening.
Opened on:

9. SPECIAL STORAGE CONDITIONS

Before first opening: store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble "Le Wilson"
70 Avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1049/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystadrops

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Cystadrops 3.8 mg/mL eye drops solution
cysteamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 3.8 mg of cysteamine (mercaptamine), as hydrochloride.

3. LIST OF EXCIPIENTS

Excipients: benzalkonium chloride (see leaflet for further information), disodium edetate, carmellose sodium, citric acid monohydrate, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops solution

1 vial of 5 mL. Component of a multipack. Not be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Discard 7 days after first opening.
Opened on:

9. SPECIAL STORAGE CONDITIONS

Before first opening: store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases
Immeuble "Le Wilson"
70 Avenue du Général de Gaulle
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1049/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Cystadrops

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Cystadrops 3.8 mg/mL eye drops solution
cysteamine
Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

Discard 7 days after first opening.

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Cystadrops 3.8 mg/mL eye drops solution cysteamine (mercaptamine)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

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

What is in this leaflet

1. What Cystadrops is and what it is used for
2. What you need to know before you use Cystadrops
3. How to use Cystadrops
4. Possible side effects
5. How to store Cystadrops
6. Contents of the pack and other information

1. What Cystadrops is and what it is used for

What Cystadrops is

Cystadrops is an eye drops solution that contains the active substance cysteamine (also known as mercaptamine).

What it is used for

It is used to reduce the quantity of cystine crystals in the surface of the eye (cornea) in adults and children from 2 years of age with cystinosis.

What is cystinosis

Cystinosis is a rare hereditary disease in which the body is unable to remove excess cystine (an amino acid), causing cystine crystals to accumulate in various organs (such as kidney and eyes). Accumulation of crystals in the eye can lead to increased sensitivity to light (photophobia), corneal deterioration (keratopathy) and loss of vision .

2. What you need to know before you use Cystadrops

Do not use Cystadrops

If you are allergic to cysteamine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before using Cystadrops.

Other medicines and Cystadrops

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

Pregnancy and breast-feeding

Even if the level of Cystadrops in the blood is negligible, precautions should be taken.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

You may find that your vision is blurred for a few minutes just after using Cystadrops. Do not drive or use machines until your vision is clear.

Cystadrops contains benzalkonium chloride

This medicine contains 5 micrograms benzalkonium chloride in each drop which is equivalent to 0.1 mg/ml.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards.

Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use Cystadrops

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose

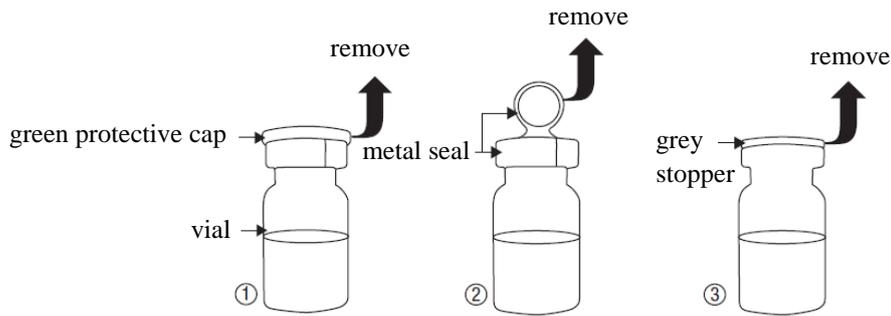
- The recommended dose is 1 drop in each eye, 4 times a day during waking hours.
- The recommended interval between each application is 4 hours (for example, you can have your eye drops at 8.00 am, 12.00 am, 4.00 pm and 8.00 pm).
- To avoid sticky eyes in the morning, it is recommended to apply the last drop of the day at least 30 minutes before going to bed.
- The dose may be gradually decreased (to a minimum total daily dose of 1 drop in each eye) by your doctor based on eye examinations.

Only use the drops in your eyes (ocular use).

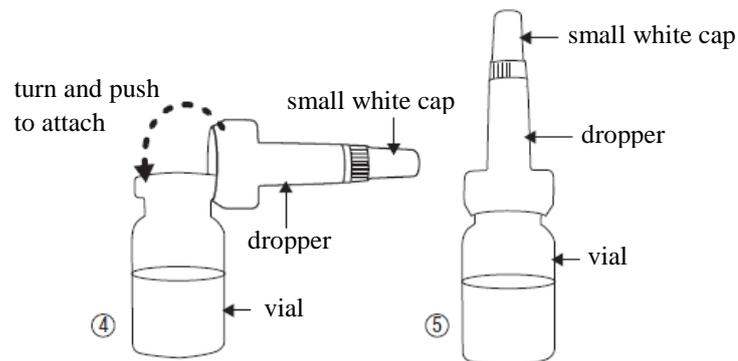
To use the eye drops, please follow the instructions below carefully. Those instructions are also available as an animated movie on www.cystadrops.net 'QR code to be included'

Step 1: Before using a vial for the first time

- Cystadrops must be brought back at room temperature before the first administration. It will facilitate the use of the drops.
- Immediately before using a vial for the first time, write the date of opening in the space provided on the carton box.
- Wash your hands carefully in order to avoid contamination by bacteria 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, and attach it (picture 4) to the vial. Do not remove the dropper from the vial.



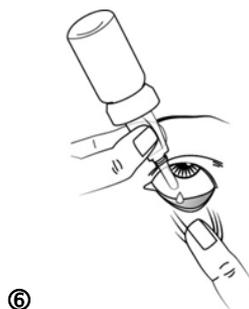
- Make sure that you do not lose the small white cap (picture 5) that comes on the top of the dropper.

Step 2: Before using the eye drops

- Check the opening date that you wrote down on the carton box. Cystadrops can be used for up to 7 days from the time of opening.
- Get the dropper bottle and a mirror.
- Wash your hands.

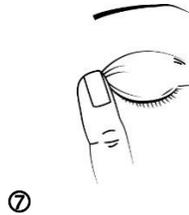
Step 3: Using the eye drops

- Hold the dropper bottle, pointing down, between your thumb and fingers. Move firmly the dropper bottle up and down to facilitate the filling of the dropper.
- Unscrew the small white cap from the dropper.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a “pocket” between the eyelid and your eye. The drop will go in here (picture 6).

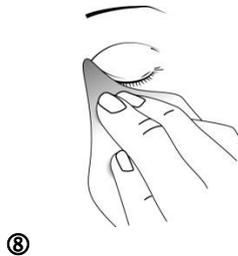


- Bring the dropper bottle tip close to the eye. Use the mirror if it helps.

- **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops.
- Gently squeeze the dropper to release one drop of Cystadrops at a time. Take special care not to touch the tip of the dropper with your fingers.
- After using Cystadrops, press a finger into the corner of your eye by the nose (picture 7), then gently massage your upper eyelid to spread the eye drops over the eye.



- To avoid potential irritation, remove excess medicine around the eye with a moist tissue (picture 8).
- Repeat the step 3 for the other eye.
- Replace the small white cap on the dropper immediately after use.



Step 4: Storing the eye drops after use

- Place the dropper bottle into the carton box.
- Keep Cystadrops at room temperature (it will facilitate the use of the dropper).
- **Discard 7 days after opening.**

If a drop misses your eye

Try again.

If you use Cystadrops with another eye medicine

Ensure that there is at least a 10 minute gap between using Cystadrops and the other eye medicine. Administer eye ointments last.

If you wear soft contact lenses

Do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

If you use more Cystadrops than you should

If you put too many drops in your eyes, rinse your eyes out, preferably with saline solution (or if not available with warm water). Do not put in any more drops until it is time for your next regular dose.

If you forget to use Cystadrops

Wait for your next scheduled application and then continue with your regular routine. Do not use a double dose to make up for a forgotten dose.

If you stop using Cystadrops

Cystadrops must be used every day for the medicine to work properly. If you stop using Cystadrops, cystine crystals accumulation in the eye (cornea) may increase and lead to increased sensitivity to light

(photophobia), corneal deterioration (keratopathy) and loss of vision. Therefore talk to your doctor before stopping this treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

You can usually carry on taking the drops, unless the effects are serious. If you are worried, talk to your doctor or pharmacist. Do not stop using Cystadrops without speaking to your doctor.

The following side effects were reported:

Very common side effects (may affect more than 1 in 10 people)

- eye pain
- eye redness, eye itching, eye irritation (burning)
- watery eyes
- blurred vision
- discomfort where the drops have been instilled (mainly sticky eyes and sticky eyelashes), medicine deposit on the eyelashes, around the eyes

Common side effects (may affect up to 1 in 10 people)

- abnormal sensation in eye, a feeling of something in the eye
- dry eyes
- swollen eyelid
- irritation of eyelid
- visual impairment
- pain where the drops have been instilled
- stye

Reporting of side effects

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

5. How to store Cystadrops

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

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

Before opening:

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

After first opening:

- Write down the date you opened the vial in the space on the carton.
- Cystadrops can be used for up to 7 days from the time of opening.
- Keep the dropper bottle tightly closed in the outer carton in order to protect from light.
- Store below 25°C.

- Do not refrigerate.
- **You must throw away the dropper bottle 7 days after you first opened it even if it is not empty.** Use a new vial.

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

6. Contents of the pack and other information

What Cystadrops contains

- The active substance is cysteamine (mercaptamine), as hydrochloride. One mL of eye drops solution contains 3.8 mg of cysteamine.
- The other ingredients are benzalkonium chloride (see section 2 under ‘Cystadrops contains benzalkonium chloride’), disodium edetate, carmellose sodium, citric acid monohydrate, sodium hydroxide, hydrochloric acid and water for injections.

What Cystadrops looks like and contents of the pack

Cystadrops is a clear and viscous eye drops solution.

Each box contains:

- 1 amber glass vial containing 5 mL of eye drops solution,
- 1 dropper applicator.

Cystadrops is available in pack containing 1 box or in multipack containing 4 boxes.

Not all pack sizes may be marketed in your country

Marketing Authorisation Holder

Recordati Rare Diseases
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Manufacturer

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Other sources of information

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