CLINICAL REVIEW NDA 211302 Class 2 Resubmission
CYSTADROPS (cysteamine ophthalmic solution) 0.37%

Application Type	NDA
Application Number(s)	211302
Submit Date(s)	February 28, 2020
Received Date(s)	February 28, 2020
PDUFA Goal Date	August 28, 2020
Division/Office	DDO/OSM
Reviewer Name(s)	Sonal D. Wadhwa
Review Completion Date	August 18, 2020
Established/Proper Name	Cysteamine ophthalmic solution
(Proposed) Trade Name	CYSTADROPS
Applicant	Recordati Rare Disease Inc.
Dosage Form(s)	Topical ophthalmic
Applicant Proposed Dosing Regimen(s)	One drop OU qid
Applicant Proposed Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of corneal cystine crystal deposits in adults and children with cystinosis

1. Summary

A Class 2 Resubmission of NDA 211302 was received on February 28, 2020, in response to the Agency Complete Response letter dated January 28, 2020:

- The facilities and controls used for, the manufacture, processing, packing, and holding of the drug product did not comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211.

- The methods to be used in, and the facilities and controls used for the manufacture, processing, packing and holding of the drug product were inadequate to preserve its identity, strength, quality, purity, stability or bioavailability.

CYSTADROPS is a cystine-depleting agent. It is a sterile viscous ophthalmic solution containing 5.6 mg/mL of cysteamine hydrochloride equivalent to 3.8 mg/mL of cysteamine (0.37%). Cystinosis is a rare and serious condition characterized by the intracellular accumulation of cystine. If not treated, cystinosis in its most severe form invariably leads to renal failure, necessitating dialysis and ultimately renal transplantation. Oral treatment with a cystine depleting agent, cysteamine, has greatly reduced the morbidity and mortality of this disease. Accumulation of cystine crystals due to cystinosis also occurs in the cornea. Due to the absence

of corneal vascularization, corneal cystine crystal deposits are minimally affected by systemic treatment with cysteamine.

Therefore, to treat the corneal crystal accumulation a topical treatment with a cysteamine containing eye drops is necessary to dissolve corneal cystine crystal deposits. If untreated topically, cystinosis can lead to the deterioration of visual capacity and eventually the need for a corneal graft.

The application for CYSTADROPS is submitted as a 505(b)(2) application listing Cystagon Capsules, NDA 20-392 as the listed drug product.

See the original Medical Officer's review in DARRTS dated 1/22/20.

The data contained in this application establishes the safety and efficacy of CYSTADROPS ophthalmic solution dosed qid for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.

2. Safety Update

On March 27, 2020, an updated Safety Report was provided with data for the reporting period from 01 November 2019 to 18 January 2020.

Cystadrops is currently licensed in 34 countries worldwide (28 European Union member states plus Canada, Columbia, Iceland, Liechtenstein, Mexico and Norway).

Severe eye irritation remains an important identified risk for Cystadrops. The important potential risks include punctate keratopathy and/or toxic ulcerative keratopathy, corneal neovascularization, ocular manifestations of Ehlers-Danlos like Syndrome, and increased risk of infection and medication error due to device assembly failure.

Review of the data collected during the reporting period and cumulative data does not reveal any new safety concerns that are not reflected in the current Risk Management Plan and prescribing information for Cystadrops; therefore, no changes to these documents are currently proposed.

The overall benefit-risk profile of Cystadrops remains favorable when the drug is used in its approved indication and duration of treatment.

Table 7: Cumulative sales of Cystadrops by region up to 18 January 2020

Region/Country	Quantity sold (b) (4)
Argentina	
Belarus	
Brazil	
Brunei Dar-es-S	
Columbia	
EU[a]	
Hong Kong	
Iceland	
India	
Japan	
Middle-East and North Africa[b]	
Norway	
Pakistan	
Russia	
Rwanda	
Serbia	
South Korea	
Uruguay	
Total	

EU=European Union.

[a] Including: Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, the Netherlands and the UK.

[b] Including: Algeria, Bahrain, Egypt, Iraq, Israel, Jordan, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, and the United Arab Emirates.

3. Recommendations

NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% is recommended for approval for the treatment of corneal cystine crystal deposits in adults and children with cystinosis. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

4. Labeling

The agreed-upon labeling for NDA 211302 CYSTADROPS (cysteamine ophthalmic solution) 0.37% is attached.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
08/18/2020 03:51:55 PM

WILLIAM M BOYD
08/19/2020 06:29:46 AM