CYSTAGON (mercaptamine bitartrate):

- **Recall of batch T2208 due to reports of hospitalisation for severe GI symptoms**
- **Reports of excessively strong odour and broken capsules with other batches**
- **proposed return to previous desiccant composition with black activated carbon**

Dear Healthcare professional,

RECORDATI RARE DISEASES in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- Eight reports of hospitalisation for severe gastrointestinal symptoms, in which an excessive bad smell was noted with Cystagon capsules have been received with a batch of Cystagon (Batch # T2208).
- As a precautionary measure RECORDATI RARE DISEASES has recalled the impacted batch (# T2208) which has to date been circulated within one EU country (Italy).
- Other reports, concerning an excessively bad smell and broken capsules, have been received for other batches of Cystagon (batch # T2207 and # T2209) including only one report of non-serious case with gastrointestinal disorders (batch # T2207).
- Investigations conducted to date on impacted batches (batch # T2207; #T2208, # T2209, # T2210 and # T2211) do not indicate a quality defect. However, a change of the composition of the desiccant is suspected.
- As a measure of correction, RECORDATI RARE DISEASES proposes to revert to the initial design of the container with a canister containing both desiccant and black activated carbon.
- In order to avoid possible shortages, batches of Cystagon produced with another drug substance supplier will be distributed. These batches are currently distributed in European countries without similar complaints.
- Batches with the previous device (containing both desiccant and black activated carbon) are expected for April 2023.

Background on the safety concern

Cystagon is indicated for patients who have nephropathic (kidney) cystinosis.

Following the distribution of batch # T2208 of CYSTAGON 150mg capsules in Turkey (for compassionate use), 8 patients experienced severe gastrointestinal symptoms leading to hospitalization just after taking Cystagon. All patients recovered. A bad smell from the Cystagon capsules was also reported in these cases. The unexpected severity of these known reactions (listed in the Product Information) and the lack of clear understanding of the root cause led the company to recall this batch in the countries where it has been distributed and to carry out a full investigation. Within the EU, the affected batch has only been distributed in Italy.

In addition, the company received several complaints regarding an excessive bad smell of the products produced at the same time (batches produced in the same facility, using the same supplier of active ingredient) (batch T2207 and T2209) and also, complaints regarding some broken capsules. Only one non-serious case with gastrointestinal disorders was reported to the company.

An investigation has been performed on the batch associated with the 8 reports of hospitalisation (# T2208) and this investigation has been extended to other batches produced at the same time (# T2207; # T2209, # T2210 and # T2211). **This investigation covering the 5 batches has not identified any quality defect.**

The only cause identified to explain the complaints received on the batches of this campaign (strong smell) is the absence of black activated carbon in the formulation which is currently marketed. At

time of the transfer of the bulk production site of CYSTAGON from USA to France in mid-2021 the 2-in-1 canister which was present in the bottles (containing black activated carbon and silica granules as a desiccant) has been replaced by a silica-based desiccant present in the container closure.

The purpose of the black activated carbon is to absorb the strong odours of cysteamine (the active principle of Cystagon and especially of cystamine, its main degradation product). The removal of the black activated carbon from the composition of the desiccant may explain these reports concerning an excessively bad smell.

Reports concerning broken capsules may be explained by a higher quantity of desiccant in the current containers (2g) compared to the previous containers containing a 1g canister with desiccant and black activated carbon which may weaken the body of the capsules.

The distribution of the of the 4 other batches (# T2207, # T2209, T 2210 and # T2211) produced at the same time of batch # T2208 has been stopped. No new case has been reported for these batches.

No additional risk related to the reporting issue with a bad smell have been established, the use of the product is considered as safe;

The aim of this letter to Health Care Professionals is:

- to inform you on the recall of one batch of Cystagon (# T2208) due to severe gastrointestinal symptoms,
- to inform you on several reports of excessively strong odour and broken capsules with other batches produced at the same time (# T2207; # T2209, # T2210 and # T2211),
- to describe the investigation performed and the absence of quality defect
- to inform you that due to the absence of a device containing activated carbon, intended to absorb odours from the container of CYSTAGON, capsules may have a very strong unpleasant smell that can be very bothersome for some patients.
- to reassure you that the benefit / risk profile of Cystagon remains positive.

Batches of Cystagon with the new device (desiccant and black activated carbon) are expected April 2023.

Call for reporting

-In case of adverse event, please contact XXX local health authorities (ADD THE QRD template reference for reporting adverse event)

Or contact the following email address: RRDpharmacovigilance@recordati.com

-In case of complaints on CYSTAGON, please send them to the following email address: RRDcomplaints@recordati.com

Company contact point

Any additional questions can be sent to: RRDmedinfo@recordati.com

EU QPPV Chief Pharmaceutical Officer

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	CYSTAGON 150 mg, hard capsules
Marketing authorisation holder(s)	Recordati Rare Diseases sarl Immeuble "Le Wilson" 70 avenue du General de Gaulle 92800 Puteaux, France
Safety concern and purpose of the communication	Very bad smell of Cystagon capsules, broken capsules, and gastrointestinal symptoms. Batch T2207 to batch T2211
DHPC recipients	All Cystagon prescribing HCPs + patients association for cystinosis. The target group would be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	As a priority, in all EU countries where the 5 batches (T2207 to T2211) have been distributed: Austria Belgium Germany Hungary Italy Netherlands Poland Spain For information in other EU countries.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP	25/01/2023
Submission of translated DHPCs to the national competent authorities for review	01/02/2023
Agreement of translations by national competent authorities	08/02/2023
Dissemination of DHPC	15/02/2023