

Quality Assurance (QA) for Health Products**QA Information Notice**

IN N° 2019-10 Version: 07/11/2019	VOLUNTARY RECALL of Batch ECF7901A of Cycloserine 125 mg Capsules, supplied by Macleods and Suspension of procurement
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Addressees

- Any person having products in stock (pharmacies, retailer) in transmit or under custom clearance
- Any procurers, buyers with a pending order

Purpose

The GF QA is issuing this information notice to provide information that was transmitted by Macleods regarding a voluntary recall (level II Class) initiated on 23rd of October 2019 for the following product.

Identification of the product(s) and manufacturer

Name of Manufacturer	Macleods
INN Name	Cycloserine
Commercial Name(s)	Cycloserine Capsules USP 125mg
Pharmaceutical form	Capsule
Strength	125 mg
Packaging & Pack size	Blister, Alu/Alu 10x10; Strip, Alu/Alu 10x10
Batch(es)	ECF7901A
Expiry Date	4/2021

Background

Prior to shipment to countries, the batch was subject to Quality control testing which was performed by SGS Netherland on behalf of the Stop TB Partnership/Global Drug Facility. An out of specification was reported for the related substance parameter. The cycloserine dimer impurity was found above the specified limit. Following investigations, the manufacturer, Macleods decided to initiate a Class II level recall (see Annex 1). The decision has been made based on the unknown toxicity of the cycloserine dimer and its impact on the bioavailability of the Finished Pharmaceutical Product.

Nature of defect(s)

Details of defect or problem.	Non-compliant results founded for related substance testing. Cycloserine dimer impurity was found above specified limit: 1.3%w/w instead of 1.0%w/w.
Is there any evidence or suspicion of a	No concrete evidence of risk for patient. Potential toxicity of the cycloserine dimer impurity, potential

risk to public health?	decrease in efficacy.
Extent of the problem (eg. how many batches).	1 batch: ECF7901A 1329 packs of 100 capsules
Extent of distribution of the product / batch (es).	Evidence of distribution to Ghana, Kenya, Malawi Mozambique, Rwanda and Zimbabwe. Worldwide distribution could be excluded.
Number of patients potentially impacted	No impacted patients known

Action/Investigations taken

- GDF identified the countries which were impacted by the OoS and provided the list to GF QA;
- The impacted quantities of this batch (ECF7901A) procured through GDF (e.g. 1.329 packs) were requested to be quarantined at Wholesaler and country level. (see Annex 2 for details);
- GF investigated and could confirmed that no direct procurement occurred for this Batch number.
- GDF and GF to forward the information regarding this recall, using this QA Information Notice, to the wholesaler and Countries respectively.

Next Steps

Based on the information available to date and until further notice, the following actions are recommended by GF QA:

- To put immediately in quarantine conditions the impacted products at pharmacy and retail level of the supply chain and send it back to wholesaler/regional or central distributors;
- not applying to user level;
- To stop immediately any shipment and further distribution of the impacted product within the supply chain (wholesaler/regional or central distributors);
- To report or confirm to the supplier/procurer the stock put in quarantine conditions;
- To suspend the procurement of Cycloserine 125mg capsules from Macleods until further notice.

Contacts

This IN does not require specific written response from PR. PRs should copy GF QA Team of any correspondence regarding the matter for follow-up.

Please direct the respective answers and any questions about this matter to the technical contacts listed below:

Organisation	Name / Function	E-mail address
Global Fund	Amelie Darmon, Associate QA Specialist	Amelie.Darmon@theglobalfund.org
Global Drug Facility	Nigorsulton Muzafarova, Lead Product Quality Officer	nigorsultonm@stoptb.org

Annex 1: manufacturer's recall letter

**Recall Intimation Sheet****1. PRODUCT INFORMATION****a. Product Name (Generic Name) :**

Cycloserine Capsules USP 125mg

b. Description of the Product :

i. Dosage Form: Capsules

ii. Indications: Cycloserine is used to treat tuberculosis (TB) caused by Mycobacterium tuberculosis. It is always given together with other medicines for TB. Cycloserine belongs to the family of medicines called antibiotics.

iii. Shelf Life : 24 months

iv. Packing : 10 X 10's Blister Pack

v. Labeling in electronic form: Package Insert is attached as **Annexure-I**.

vi. Strength : 125 mg

vii. Route of Administration : Oral

2. PRODUCT IDENTIFICATION NUMBERS

Lot/ Unit Numbers	Mfg Date	Expiration Date
ECF7901A	May 2019	April 2021

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**MACLEODS
PHARMACEUTICALS
LIMITED**

Regd. Office :
Atlanta Arcade, Church Road,
Near Leela Hotel, Andheri-Kurla Road,
Andheri (East), Mumbai-400 059, India.

Phone : 91 - 22 - 6676 2800
Fax : 91 - 22 - 2925 6599
Email : customercare@madeodspharma.com
Website : www.macleodspharma.com
CIN : U24239MH1989PLC052049

Works :
G-2, Mahakali Caves Road,
Shanti Nagar, Andheri (East),
Mumbai 400 093, INDIA
Phone: +91 22 61132900



3. RECALLING FIRM

a. **Firm Name, Address, City, State, Zip Code:**

Macleods Pharmaceuticals Limited, 304, Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai, Maharashtra (State), India – 400059.

b. **Identify Firm Type:** ANDA Holder and manufacturer.

c. **CONTACTS for Recalling Firm:**

i. Recall Contact : Mr. Jayaram K.R., Vice President – Corporate Quality Assurance,

Macleods Pharmaceuticals Limited,
G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai - 400093, INDIA, Phone: + 91 22 61132900, Fax: 91 22 28304641, e-mail: jayaramk@macleodspharma.com

ii. Most Responsible individual : Mr. M.R. Sarde – Site Head Operations

India Contact Location Address:

Macleods Pharmaceuticals Limited,
Macleods Pharmaceuticals Limited, Plot No. 25-27, Premier Industrial Estate, Kachigam, Daman - 396210 India, Phone: + 91 -0260-2240125, 2244337, Fax :+ 91 -260-2241565
e-mail: sarde@macleodspharma.com

4. RECALL COMMITTEE

Sr. No.	Name of the Person	Designation	Department	E-mail ID	Office Nos.	Mobile Nos.
1	Mr. K R Jayaram	Vice President CQA	Corporate QA	jayaramk@macleodspharma.com	+91 22 61132900	+919152730648
2	Mr. M. R. Sarde	Assistant Vice President	Operation	sarde@macleodspharma.com	+ 91 -0260-2240125, 2244337	+919974091632
3	Mr. Nishat Ahmad	Sr. General Manager	Site Quality Assurance	nishata@macleodspharma.com	+ 91 -0260-2240125, 2244337	+919662018697
4	Mr. Vijay Agrawal	Business Development Director	H.O.	vijay@macleodspharma.com	+91-2261132900	+919820804126
5	Mr. S. B. Parhi	Deputy General Manager	Production	parhis@macleodspharma.com	+ 91 -0260-2240125, 2244337	+917574802005
6	Ms. Sandhya Jadhav	Sr. Manager	Regulatory Affairs	sjadhav@macleodspharma.com	+91 22 61132900	+917777015309
7	Dr. Ashish MungatIwar	Executive Vice President – PV group	Pharmacovigilance Department	drashish@macleodspharma.com	+91-2266762800	+919867023914

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5. MANUFACTURER:

- a. Macleods Pharmaceuticals Limited, Plot No. 25-27, Premier Industrial Estate, Kachigam, Daman – 396210, India.

6. FIRM RESPONSIBLE FOR VIOLATION/ PROBLEM:

- a. Macleods Pharmaceuticals Limited, Plot No. 25-27, Premier Industrial Estate, Kachigam, Daman – 396210, India.

7. REASON FOR RECALL:

The recall of the subject batch is being initiated due to the determination of out of specification result in Related Substance Test by SGS Life Sciences, India. When it was re-tested on 24/08/2019 by SGS Life Sciences, India; results of 1.3% obtained for Cycloserine Dimer impurity against the specification limit of NMT 1.0 % and result of 1.5% was obtained for Total Impurities against the specification limit of NMT 1.5%.

The result for Cycloserine 125 mg capsules batch # ECF7901A was complying with the related substances test during its Finished Product Release. The batch also found complying with the specification at the 3M stability study time point.

However the recall is being initiated due to the OOS results reported by the SGS Life Sciences, India.

The details of the results are reported in below tablet:

Stage	Related substances									Assay Limit 92.5 - 107.5%
	Dimer Impurity NMT 1.0%				SMI NMT 0.2%		Total unknown		Total Impurities NMT 1.5%	
	Dimer 1	Dimer 2	Sum	%	Area	%	Area	%	%	%
FP release	3925	16904	20829	0.237	42523	0.03	84978	0.06	0.27	102.1
SGS	42976	72572	115548	1.333	104120	0.07	235285	0.15	1.5	96.8
Stabil ity 3M	30872	56046	86918	0.90	95732	0.06	127196	0.15	1.05	94.3

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Based on preliminary investigation following probable causes were identified for the above reported failure:

1. The product would have got exposed to the elevated temperature / humidity either during packaging or during storage which may lead to failure in related substances test A, as this impurity increases at high temperature and high humidity; same is proved in forced degradation study.
2. Based on the review of results reported for API batches using Finished Product test procedure, higher Dimer impurity in the API batch could have lead to increase in impurities in finished product on storage.
3. Results reported at SGS laboratory are higher as comparable with the results reported at Macleods site. The probable cause for this difference could be due to analytical variation. The Dimer impurity is eluting at the tailing of the Cycloserine peak. Column flushing or mobile phase separation can have impact on the separation of impurities and lead to variation in the results. Also, pH plays critical role in conversion of Dimer from Cycloserine.

Further the full scale investigation is on-going.

8. CORRECTIVE AND PREVENTIVE ACTION:

- As an immediate corrective action we are voluntary recalling the batch ECF7901 of product Cycloserine Capsules USP 125 mg from the market.
- Further the production of Cycloserine Capsules USP 125 mg has been put on hold.

9. HEALTH HAZARD ASSESSMENT

The results for assay and related substances analysis at 3rd month at 25°C / 60% RH for batch ECF7901A was found within the specification. However during analysis at SGS lab the dimer impurity (1.33%) found to increase drastically and does not comply with the acceptance criteria as per pharmacopeial procedure. Also unknown impurities found to increase. There are no literatures available about the impact of Dimer impurity of Cycloserine on the bioavailability of the product nor its toxicological data. Hence it is less likely to affect therapeutic activity of Cycloserine and less likely to pose the risk to patient safety. Refer Attached **Annexure-II**.



10. VOLUME OF RECALLED PRODUCT

S. No.	Details	Batch # ECF7901A
1.	Theoretical batch size	150000 Capsules
2.	Date produced	Mfg Start Dt - 2 May 2019 Pkg End Dt - 14 May 2019
3.	Total quantity produced	135700 Capsules 1357 Packs 10 x 10's
4.	Control / retention samples	400 Capsules 4 Packs 10 x 10's
5.	Sample for COA generation	50 Capsules 5 Blister
6.	Stability sample	1160 Capsules 11 Packs and 6 Blister
7.	Micro sample	90 Capsules 9 Blister
8.	Quantity released	134000 Capsules 1340 Packs
9.	Regulatory Sample RA/PDR/ARD samples	9 Packs of 10 x 10's = 900 Capsules
10.	SGS inspection agency taken as samples	2 Packs of 10 x 10's = 200 Capsules
11.	Date of dispatch	1. Invoice No. J0434 dispatch from plant to central warehouse 25.05.19. From central warehouse to Netherland 03.06.19. 2. Invoice No. J0434 dispatch from plant to central warehouse 14.06.19. From central warehouse to Netherland 27.06.19. 3. Invoice No. J0434 dispatch from plant to central warehouse 09.07.19. From central warehouse to Netherland 20.08.19.
12.	Total quantity dispatched	1329 Packs of 10 x 10's = 132900 Capsules
13.	Quantity distributed in Market	1264 Packs of 10 x 10's = 126400 Capsules

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S. No.	Details	Batch # ECF7901A
14.	Non- commercial stock (released but non distributed - Under Quarantine at Netherlands with IDA)	65 Packs of 10 x 10's = 6500 Capsules

11. DISTRIBUTION PATTERN


The goods are dispatched from manufacturing site to importer IDA Foundation. The product is distributed further by IDA Foundation.

12. RECALL STRATEGY:

- a. Level of Recall: Class II Level Recall. Product shall be recalled up to Pharmacy / Retailer level.
- b. Method of Notification: Letters will be sent via email to the IDA where we shipped the Lot # ECF7901A. Specimen Recall Notification Letter is provided as **Annexure -III**. IDA will further notify its customers upto Pharmacy / Retail level.
- c. Effectiveness check strategy
 - i. Reconciliation of distributed stock shall be carried out against the returned stock.
 - ii. Confirmation shall be obtained that they have returned the complete stock and that they do not possess any remaining stock of these batches.
- d. Multiple modes of communication, which includes e mail, phone and written notification to wholesalers/ retailers / pharmacies.
- e. Mode of destruction: Returned goods shall be destroyed by IDA as per prevalent regulations.
- f. No product shall be re-conditioned.



You may contact the undersigned if you have any questions regarding this report.


23/05/2019

Sincerely,

Jayaram K.R.,

Vice President - Corporate Quality Assurance

Macleods Pharmaceuticals Limited,

G-2, Mahakali Caves Road, Shanti Nagar,

Andheri (East), Mumbai - 400093, INDIA

Phone: + 91 22 61132900 Fax: 91 22 28304641

e-mail : jayaramk@macleodspharma.com

Annex 2: GDF distribution list

Order reference	Country	Quantities in packs (100 caps)	Quarantine status YES/NO	Location of the consignment
KEN/DP/19/8545-19200269 KEN/DP/19/8547-19200293	Kenya	152 159	YES	Amsterdam, IDA DBS
MOZ/DP/18/8260- 18201703 MOZ/DP/18/8433/ 19200233	Mozambique	410 494	YES	Amsterdam, IDA DBS
ZWE/DP/18/8352-19200145	Zimbabwe	50	YES	In country
MWI/DP/19/8567-19200217	Malawi	15	YES	In country
RWA/SF/19/8704-19200891	Rwanda	10	YES	In country
GHA/DP/19/8916-19200956	Ghana	39	YES	Amsterdam, IDA DBS