Kigali on; 07/10/2021
Ref N°: DIS/ 3261 /FDA/2021

RWANDA FDA
Rwanda Food and Drugs Authority
P.O. Box 1948 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

Public and private Health facilities (All)
Central medical stores (All)
Pharmaceutical Wholesalers (All)
Importers (All)
Retail Pharmacies (All)
District pharmacy (All)
Public (All)

Title: Voluntary Recall for all batches of Losar-Denk (Losartan) and Colosar-Denk (Losartan/ hydrochlorothiazide)

Reference is made to the Law N° 003/2018 of 09/02/2018 establishing Rwanda Food and Drugs Authority especially in its article 8 paragraph 2 and 13. Reference is also made to the regulation No CBD/TRG/019 governing recall, treatment and disposal of unfit products. Further reference is made to the voluntary recall date 4th October 2021 issued by Denk PharmaGmbH and Co.KG. Denk Pharma recall indicates that previously unknown impurity called '4-chlor-Azidomethyltetrazole' (CAS: 727718-93-6) was detected in the active pharmaceutical ingredients (API) losartan potassium from two API manufacturers. According to the current information, the impurity can only be formed during the production of the active ingredient losartan, and has been found in the active ingredient of at least three API manufacturers (CEP Holders).

The performed test results by Germany Authority indicate that the presence of the impurity in API Losartan potassium used in Denk Pharma finished products are above Threshold Toxicological Concern (TTC) but still investigations are ongoing.
After analysis of the above information, Rwanda FDA informs that all batches of Losar-Denk (Losartan) and Colosar-Denk (Losartan/Hydrochlorothiazide) described below are recalled from the Rwandan market:

- **Losar-Denk 25mg firm-coated tablet, all batches** (including free samples, if available)
- **Losar -Denk 50 mg film-coated tablet, all batches** (including free samples, if available)

- **Losar-Denk 100 mg film-coated tablet, all batches** (including free samples, if available)
- **Colosar-Denk 50 mg / 12,5 mg film-coated tablet, all batches** (including free samples, if available)
- **Colosar-Denk 100/12,5 mg film coated tablet, all batches** (including free samples, if available)

Action to be taken

- Rwanda Food and Drug Authority instructs all importers, central medical stores, wholesalers, District Pharmacies, retail pharmacies, Public and Private Health Facilities to stop the distribution and dispensing of the above incriminated medicines (Lozar-Denk and Colozar-Denk) and return them to the suppliers for suitable management.
- The importers and Suppliers of the incriminated medicines (Lozar-Denk and Colozar-Denk) are requested to report to Rwanda FDA within 10 working days, the quantities imported, quantities distributed, quantities returned and final stock on hand.
- Patients under treatment with the above mentioned medicines are recommended not to discontinue their medications without first consulting their attending physician

Note: For more information or to report any suspected poor quality products please call 9707 or send email to: pv_sm@rwandafda.gov.rw

Sincerely,

07/10/2021

Dr. Emile BIENVENU
Director General

DENK PHARMA GmbH & Co. KG · Prinzregentenstr. 79 · D-81675 München

To whom it may concern

Kontakt/Contact
losartan@denkpharma.de

Datum/Date
04.10.2021

Recall of Losar-Denk and CoLosar-Denk, all batches

Dear Madam or Sir,

Recently the responsible European Health authorities have informed **Denk Pharma GmbH & Co. KG** about the detection of a previously unknown impurity called *"4-Chlor-Azidomethyltetrazole"* (CAS: 727718-93-6) in the active pharmaceutical ingredient (API) Losartan potassium from two API manufacturers (CEP-Holders). This impurity has been newly detected and previously not been tested in the API. According to current information, the impurity can only be formed during the production of the active ingredient losartan, and has been found in the active ingredient of at least three API manufacturers (CEP Holders).

Because the impurity has been classified as genotoxic due to testing positive in a AMES test, which is a mutagenicity test performed in bacteria, and despite the fact that there is no clinical or in vivo model data available on the impact this impurity could have in humans, Denk Pharma GmbH & Co. KG has immediately conducted investigations of this impurity to determine the best course of action.

During the course of this investigation, we were informed by our German authority about the test results performed by the Official Medicines Control Laboratory (OMCL) that indicate the presence of the impurity in the API Losartan potassium used in Denk Pharma finished products that are above the Threshold of Toxicological Concern (TTC) limit of 10 ppm as outlined in ICH M7 [1].

Denk Pharma GmbH & Co. KG has the responsibility to put patient's safety first and has always committed to providing German quality standards to patients all over the world. For this reason, and **as a precautionary action**, we decided to initiate a **voluntary recall** of all potentially affected batches of Losar-Denk (Losartan) and CoLosar-Denk (Losartan / Hydrochlorothiazide) according to your national guidelines:

- **Losar-Denk 25 mg film-coated tablet, ALL batches** (including free samples, if available)
- **Losar-Denk 50 mg film-coated tablet, ALL batches** (including free samples, if available)
- **Losar-Denk 100 mg film-coated tablet, ALL batches** (including free samples, if available)
- **CoLosar-Denk 50 mg / 12,5 mg film-coated tablet, ALL batches** (including free samples, if available)
- **CoLosar-Denk 100 mg / 12,5 mg film-coated tablet, ALL batches** (including free samples, if available)

We kindly ask you to:

- Immediately stop selling the affected products and put all remaining stocks into quarantine.
- Inform your customers about the recall as per your local regulatory requirements / national guidelines.
- Please confirm the receipt of this letter until **07-Oct-2021.**
- Please provide us with the quantity of recalled products as soon as possible.
- The recalled and quarantined products shall be destroyed in line with your local requirements. Please provide a confirmation on the destruction, including quantities, as soon as possible.

Denk Pharma

Denk Pharma will **cover the costs related to the recall, including costs of destruction and the value of the goods.** Therefore it is of utter importance that you provide us the requested information **as soon as possible but the latest by 31-Dec-2021** in order to file a credit note. The attached recall form or equivalent may be used.

To our current knowledge the detected impurity has been found in the active ingredient of at least three API manufacturers and recalls of finished products have been initiated in other regions over the world, such as Germany and North America [2]. Denk Pharma is screening numerous manufacturers of the API to ascertain if it is possible to acquire an API without the mentioned impurity. Should a potential supplier become available who is proven to not have this or any related impurity, we will endeavor to provide the finished product again as quickly as possible.

Up to now, Denk Pharma GmbH & Co. KG has not received any reports of genotoxicty adverse events that could potentially be related to this impurity. The German Federal Institute for Drugs and Medical Devices (BfArM) [3], has communicated that the preliminary toxicological assessments indicate a significantly lower health risk for this impurity compared to nitrosamines. **Based on the data available, the risk of untreated cardiovascular disease may outweigh the potential risks of this identified impurity and it is recommended that patients not discontinue their medications without first consulting their attending physician.**

We appreciate your continued trust and confidence in Denk Pharma GmbH & Co. KG and express our deepest regret about this incident. Our greatest obligation is towards our patients, whether in Germany or in any of the numerous countries to which we export. For this reason we decided to be proactive and initiate this voluntary recall.

Yours sincerely,

DENK PHARMA GmbH & Co. KG

Stephan Huber
Managing Director

Dr. Fernando Guzman
Head of Medical Affairs

Prinzregentenstr. 79 · 81675 München · Germany
DENK PHARMA GmbH & Co. KG
Denk Pharma

References:

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf
[2] Canada: https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/search-recherche/result-resultat/en?search_text_1=losartan;
Singapore: https://www.hsa.gov.sg/announcements?contenttype=Product%20Recalls
[3] https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RI/2021/RI-losartan.html