Statement from the Pediatric Endocrine Society Drug & Therapeutics Committee Regarding
Recall of Extended Release Formulation of Metformin Hydrochloride

On May 28, 2020 the FDA released an alert to patients and health care professionals on nitrosamine impurity findings in certain metformin extended-release (ER) products. Laboratory testing revealed the presence of the nitrosamine impurity N-Nitrosodimethylamine (NDMA) above the acceptable intake limit in several lots of tested metformin extended release (ER) formulation (1).

NDMA exposure is common as it is a frequent environmental contaminant found in water and foods, including vegetables, dairy products and meats. NDMA can be found in drugs for multiple reasons. The source of NDMA may be related to the manufacturing process, the chemical structure of the drug, or the conditions in which they are stored or packaged.

Exposure to nitrosamine impurities above acceptable limits for prolonged periods may increase risk of cancer. However, when ingested at low levels even over long periods of time, the FDA and international scientific community does not expect harm. It is also not believed that short-term exposure above the acceptable intake limit would increase cancer risk. Additional information about NDMA toxicology can be obtained from the Agency for Toxic Substances and Disease Registry. (2)

In late 2019 the FDA announced that they were aware of NDMA in some metformin products in other countries. This prompted the agency to begin testing metformin products in the US. Once contamination was found in US metformin products, the FDA released their announcement and the agency contacted and recommended a voluntary recall by the companies making these products. As of June 11th, five companies manufacturing extended release (ER) metformin have recalled their products of selected or all lots: the manufacturers are Apotex Corp., Amneal Pharmaceuticals LLC, Marksans Pharma Limited, Lupin Pharmaceuticals Inc, and TEVA Pharmaceuticals USA, Inc. The 500 mg tablet has been recalled by all of these companies and the 750 mg product has been recalled by Teva and Amneal Pharmaceuticals. All affected lots are being taken off the shelf immediately. Statements released by manufacturers address how patients, distributors and retailers are being notified. While some manufacturers have stated plans to directly inform consumers about the recall, others have not specified such plans. It is unclear whether all affected consumers will be informed directly about this development.

The FDA is continuing to recommend that all manufacturers of metformin ER test each batch for possible NDMA contamination before it is released into the US market. There are additional manufacturers of metformin ER formulation whose products are not being recalled.

Assessments are underway to determine whether these recalls will result in drug shortages. No shortages have been reported as of the date of this document. However, this is a developing situation and the above information may change over time. The FDA and ASHP websites can be monitored for potential future shortages (3,4).

Please note that NDMA contamination has not been found in immediate release (IR) metformin products.

The FDA recommends that patients taking metformin ER continue with this treatment until they are able to consult with their healthcare professional and are prescribed alternative therapy.
REFERENCES:


3. https://www.ashp.org/Drug-Shortages/Current-Shortages (last accessed on June 14th 2020)

4. https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm (last accessed on June 14th 2020)

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