Collaborative Care Network
Expert Clinical Recommendation

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Latest FDA Recall: Metformin ER

The FDA has asked five pharmaceutical firms to voluntarily recall certain metformin extended-release lots due to higher than acceptable levels of N-Nitrosodimethylamine (NDMA).

- Apotex (all lots)
- Amneal (all lots)
- Marksans—labeled as TimeCap (one lot, XP9004)
- Lupin (one lot, G901203)
- Teva—labeled as Actavis (14 lots)

See the FDA press release on the recall here.

What is NDMA?

NDMA belongs to a group of compounds known as nitrosamines. Nitrosamines are classified by the WHO's International Agency for Research on Cancer as probable human carcinogens. The FDA, in collaboration with regulatory agencies around the world, have set acceptable daily intake limits for nitrosamines. For NDMA, the daily intake limit is 0.096 mcg. Recently, multiple medication recalls have been initiated because of unacceptable amounts of nitrosamines (e.g. angiotensin receptor blockers, ranitidine, and metformin ER). The FDA has released the laboratory test results for the metformin ER products.

Tips for discussing metformin ER recall with patients

1. Emphasize that the active ingredient, metformin, is not carcinogenic

The FDA has concluded that the source of the NDMA is not from the active pharmaceutical ingredient and that it is possible to manufacture metformin extended-release products without the NDMA impurities.

No metformin immediate-release products have had higher than acceptable levels of NDMA detected. Additionally, there are companies that manufacturer a substantial portion of metformin ER for the U.S. market whose products have not been shown to contain NDMA above the threshold.

2. Help put the risk of NDMA into context by explaining that this substance is commonly found in foods we consume every day

Nitrosamine compounds are commonly found in low amounts in water and foods including cured and grilled meats, dairy products, and vegetables. Everyone ingests some amount of nitrosamines.

For NDMA, the acceptable daily intake limit is estimated to confer a 1 in 100,000 risk of causing cancer after 70 years of exposure. Consuming this amount of NDMA every day over a lifetime is considered reasonably safe for human consumption.

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3. Reassure the patients that the metformin ER tablets that have not been recalled are safe for consumption.

New technology that allows for detection of trace amounts of impurities and knowledge on previously unrecognized risks to quality and safety in the pharmaceutical industry led to the discovery of nitrosamines in pharmaceuticals. Now, the FDA has developed, validated, and made publicly available methods to detect eight different nitrosamines.

The FDA is asking all companies manufacturing metformin ER to test at-risk product for NDMA. If testing shows levels above the acceptable limit, the company must inform the FDA and not release the batch to the U.S. market

4. Inform the patient that the FDA and American Diabetes Association (ADA) recommend patients continue to take metformin as prescribed.

The official statement from the ADA echos the FDA's recommendations:

- Patients taking recalled metformin ER should continue to take it until their pharmacy provides a replacement from a different lot
- Health care professionals should continue to prescribe metformin when clinically appropriate

5. Take this as an opportunity to review the benefits of metformin with the patients.

Metformin continues to be first-line therapy for the treatment of type 2 diabetes because of glycemic efficacy, absence of weight gain and hypoglycemia, decreased cardiovascular events in certain populations, general tolerability, and low cost

If a patient refuses to continue metformin ER despite education that it is safe, what substitution should be made?

First consider switching the patient from the extended-release formulation to the immediate-release formulation, which has not had any recalls. In a randomized, double-blind, head-to-head trial metformin ER and metformin IR were shown to have similar efficacy and safety profiles. Titrate the metformin IR slowly to avoid GI distress.

If metformin IR is not an option, follow the ADA guidelines for drug-specific and patient factors to consider when selecting an alternative antihyperglycemic agent.

After switching the medication, follow-up with an A1C at an appropriate interval to ensure that the new regimen is efficacious.

What resources are available to stay up-to-date on medication recalls?

- Sign-up to receive email updates from the FDA on recalls and drug shortages
- Follow @FDArecalls on Twitter for medication, device, and food recalls