A MEDTRUTH GUIDE

Zantac

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Zantac, The Everyday Antacid, May Be Carcinogenic

Ranitidine and nizatidine, known respectively by their brand names Zantac and Axid, are commonly used drugs to treat heartburn, gastroesophageal reflux disease (GERD), and other stomach ulcer diseases.

Earlier this year, an online pharmacy reported that they detected N-nitrosodimethylamine (NDMA) in ranitidine drugs on the U.S. market. After a preliminary investigation, the Food and Drug Administration (FDA) called for voluntary recalls of both ranitidine and nizatidine drugs that had unsafe levels of NDMA.

What is Zantac?

Ranitidine is one of the most commonly used drugs in the United States, accounting for well over fifteen million prescriptions and hundreds of millions of dollars in sales as over the counter purchases.

Ranitidine and nizatidine are drugs that treat conditions related to aggravation of stomach acid that can eat away at the lining of the stomach and throat and cause irritation, pain, damage to body tissues. Both drugs can be found as prescriptions for long term issues requiring higher doses or as over the counter drugs for short term issues requiring lower doses.

With rising rates of obesity and the prevalence of higher fat diets and larger portion sizes, increasing numbers of Americans are experiencing heartburn or are developing GERD from chronic exacerbation by stomach acid. While not nearly as commonly used as ranitidine, nizatidine is also experiencing a similar rise in usage rates by patients.

How Zantac Works

Ranitidine and nizatidine are both histamine H2 receptor antagonists. These drugs work by blocking histamine from connecting with their receptors and preventing them from triggering. The end result is a decrease in the secretion of stomach acid, and relief from conditions like heartburn, GERD, and stomach ulcers.

NDMAs and Exposure

When NDMA is consumed by humans, it undergoes a transformation in the liver into a molecule that can damage DNA and with long term exposure lead to the development of cancer. NDMA has been linked[1] to both gastric and colorectal cancers.

NDMA most often occurs as a byproduct of industrial processes. The precursor to NDMA can leach into drinking water sources, where water treatment by chlorination can convert it to NDMA. NDMA does not degrade easily and requires additional careful treatment to remove from water sources. NDMA can also enter water sources as a pesticide contaminant.

NDMA is also found in significant levels in tobacco smoke and chewing tobacco products, and in lower levels in cured meats, cheeses, beer, vegetables, and other foods.

NDMA has not been found in ranitidine and nizatidine products at a high enough level to cause immediate adverse effects, but it has been found in these products beyond the safe daily limit for carcinogenic exposure. Long term exposure to these NDMA contaminated products would place a patient at a higher risk for developing cancer.

WHO Statement on NDMAs

NDMA, also known as dimethylnitrosamine (DMN), is an organic compound that is classified by the FDA and the International Agency for Cancer Research of the World Health Organization as a probable carcinogen[2] for humans. NDMA was labelled as a probable carcinogen after trials on rats demonstrated the development of tumors after long term exposures. NDMA can also be toxic if consumed in extreme amounts.

History of Zantac Regulation

Ranitidine was created in the 1970s by the Glaxo pharmaceutical company (now known as GlaxoSmithKline) as an improvement over cimetidine, with fewer adverse effects and better and longer therapeutic effects.

Nizatidine was created in the 1980s by the pharmaceutical company Eli Lily, likely being the last of the histamine H2 receptor antagonists discovered before the advent of proton pump inhibitors, which treat the same conditions.

The FDA started a preliminary investigation after being alerted by online pharmacy company Valisure that several ranitidine products had detectable and unsafe levels of NDMA.

On September 13, the FDA issued their first alert[3] to the public that their initial tests had confirmed detection of NDMA in ranitidine products, but stated that levels were within safe thresholds. They initially attributed NDMA contamination of ranitidine products to possible manufacturing issues. Following that first alert, the FDA began issuing a series of alerts about voluntary recalls by pharmaceutical companies and distributors as they continued their testing of ranitidine products.

On October 2, the FDA issued an update that stated further testing of ranitidine found unacceptable levels of NDMA. They also stated that testing methods used by third party laboratories that were intended to test for NDMA in angiotensin II receptor blockers (ARBs) were not appropriate for ranitidine testing. In their statement they reiterated that they had issued an alternative testing method[4].

FDA Actions on Zantac

On October 23, the FDA issued another alternative testing method and reemphasized alternatives to ranitidine that are available over the counter.

On November 1, the FDA issued their longest statement to date[5], commenting that "through our testing so far, we have found levels of NDMA in ranitidine that are similar to the levels you would expect to be exposed to if you ate common foods like grilled or smoked meats." The FDA tested ranitidine products under conditions found during digestion in the human body and determined no new formation of NDMA from ranitidine, supporting their initial assertion that NDMA might be due to manufacturing issues. They also expanded their testing to nizatidine products.

However, in the accompanying November 1 release of laboratory testing results[6] the FDA had collected so far, several ranitidine and nizatidine products had levels of NDMA well above acceptable daily levels. The FDA declined to issue a mandatory recall, instead continuing to rely on voluntary recalls by pharmaceutical companies.

Patient Recommendations

The FDA so far has only found concerning levels of NDMA in ranitidine and nizatidine products. With a voluntary recall, patients are dependent on manufacturers or distributors to test their products and withdraw them if NDMA contamination is found. Major drugstore chains like Walmart, Walgreens, and CVS have already withdrawn Zantac and generic versions of ranitidine.

The FDA currently lists the following drugs as NDMA-free: famotidine (Pepcid), cimetidine (Tagamet), esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec). Due to greater side effects, it is advised that cimetidine not be used as a first choice alternative to ranitidine or nizatidine.

FDA Statement on Zantac

Until the FDA issues new guidance on the state of ranitidine and nizatidine products, the FDA has suggested that patients seek alternatives to treat heartburn, GERD, stomach ulcers, and related conditions.

In addition to drug alternatives, patients might also find it helpful to use antacids such as Tums to help relieve heartburn. Changes to diet like reducing oversized or high fat meals, alcohol, and spicy foods can also help prevent aggravation of stomach acid-related conditions.

NDMA can be detected by testing blood and urine samples, and if patients are concerned about exposure to unsafe levels of NDMA they should discuss testing with their physician.

References:

1. https://www.ncbi.nlm.nih.gov/pubmed/27188372

2. https://www.who.int/water_sanitation_health/dwq/chemicals/ndmasummary_2ndadd.pdf

3. https://www.fda.gov/safety/medical-product-safety-information/zantac-ranitidine-safety-information-ndma-found-samples-some-ranitidine-medicines

4. https://www.fda.gov/media/130801/download

5. https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs

6. https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine

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