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THE RANITIDINE CONTROVERSY (FROM BLOCKBUSTER TO BAN)

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ABSTRACT

Ranitidine, a commonly used medication for managing heartburn, acid reflux, and ulcers, became the focus of a global health debate in 2019. Sold under various brand names, including Zantac, the drug was discovered to contain or generate Nnitrosodimethylamine (NDMA), a substance classified as a probable human carcinogen, under certain conditions or during storage. Investigations revealed that NDMA levels could increase over time or when exposed to heat, raising serious concerns about its long-term safety. Regulatory bodies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) responded by issuing warnings, initiating recalls, and eventually banning ranitidine in several countries. This controversy brought attention to issues surrounding manufacturing standards, testing protocols, and the regulation of pharmaceutical impurities. It highlighted the critical importance of stringent drug safety monitoring, the complexities of addressing public health risks, and the broader implications for patient confidence and healthcare systems. The ranitidine case underscores the necessity of transparent scientific investigation and proactive measures to safeguard the safety and effectiveness of medications.

KEYWORDS: Ranitidine, Peptic Ulcer, NDMA, Cancer Risk, Histamine.

INTRODUCTION

The twentieth century witnessed the widespread occurrence of peptic ulcers, a chronic condition that affects up to 10% of the global population. Peptic ulcers are sores that form on the lining of the stomach, the duodenum (part of the small intestine), and sometimes the

esophagus. Although the link between bacteria and peptic ulcers was not widely accepted at first, Greek general practitioner John Lykoudis began treating ulcer patients with antibiotics as early as 1958. In 1982, Australian researchers Robin Warren and Barry Marshall identified Helicobacter pylori as a major factor contributing to ulcers. Their research showed that this bacterium colonizes the stomach and is responsible for causing most cases of gastric ulcers and gastritis. Infections, particularly by this bacterium, are now recognized as the leading cause of peptic ulcers.[1]

N-nitrosodimethylamine (NDMA) is a recognized environmental pollutant present in water, various foods (including dairy products, vegetables, and grilled meats), and in several industrial activities.[2,3] No research has been conducted on the carcinogenic effects of NDMA in humans following oral exposure. However, numerous animal studies have shown that NDMA can be carcinogenic.[4] The International Agency for Research on Cancer (IARC) has classified NDMA as a probable human carcinogen (group 2A).[5] Ranitidine, a widely used H2-receptor antagonist (H2RA), helps reduce gastric acid production in patients with gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD).[6] In September 2019, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency reported the presence of NDMA in Zantac®, a brand name for ranitidine. The FDA had established an acceptable daily intake limit for NDMA at 0.096 micrograms (0.32 ppm) in ranitidine. However, tests revealed that some ranitidine products contained NDMA levels up to nine times higher than this limit. As a result, many manufacturers and retailers worldwide voluntarily recalled ranitidine products. Soon after, NDMA was also found in another antihistamine, nizatidine.[7]

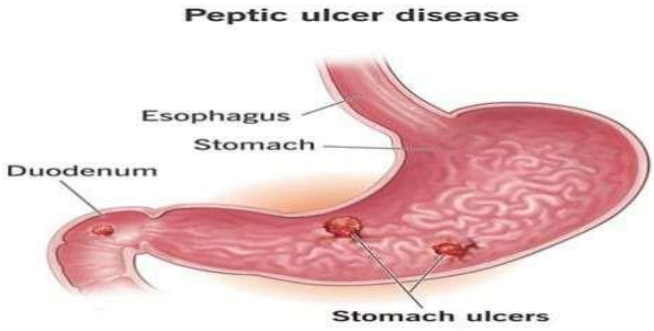

Fig. No.1: peptic ulcer.

History and Development of Ranitidine

In an effort to replicate the success of Smith, Kline, and French (now part of GlaxoSmithKline) with their first histamine H2-receptor antagonist, cimetidine, ranitidine was initially developed by Glaxo (now GlaxoSmithKline). The creation of ranitidine was the result of a methodical drug-design process, utilizing the established model of quantitative structure-activity relationships (QSAR) and the histamine H2 receptor. By incorporating a furan ring with a nitrogen-containing substituent to replace cimetidine's imidazole ring, Glaxo enhanced the concept and developed ranitidine. It was found that ranitidine was ten times more effective than cimetidine, had a better tolerability profile with fewer side effects, and provided a longer-lasting effect.

Introduced in 1981, ranitidine quickly became the top-selling prescription drug globally by 1988. However, in the years following, it was largely replaced by more potent proton pump inhibitors. Zantac, a brand name for ranitidine, was widely used to treat conditions such as Zollinger-Ellison syndrome, gastroesophageal reflux disease (GERD), and peptic ulcer disease. It could be administered orally, intravenously, or intramuscularly.

Ranitidine works by blocking the H2 receptor, reducing stomach acid production. Its molecular weight is 350.87, and its chemical formula is C13H22N4O3S. The crystalline, nearly odorless powder, known as ranitidine HCl, is white to pale yellow, sensitive to light and moisture, and melts with decomposition around 140°C.[8]

METHODS

1. Data Source

We conducted an observational population-based cohort study using the Health Insurance Review and Assessment (HIRA) database in South Korea. This database contains health insurance claims data, often referred to as National Health Insurance Service (NHIS) data, as it is generated during the claims process for healthcare services in the country. The NHIS is a non-profit organization that operates as a single insurer, managing the national health insurance program. Nearly all of South Korea’s 52 million residents are required to enroll in the NHIS. The program provides extensive insurance benefits, covering in-patient and out-patient care, prescription medications, rehabilitation services, and health promotion activities. Consequently, almost all medical services are delivered under NHIS coverage, and healthcare providers submit claims for reimbursement to the NHIS. This process ensures that all relevant healthcare data are consolidated within the NHIS database.[24] The International

Classification of Disease, Tenth Revision (ICD-10) codes are utilized to identify diagnoses. For cancer patients, a specific diagnostic code (C-code) is assigned alongside the ICD-10 code. Our study focused on liver, lung, kidney, biliary tract, and prostate cancers, which have been linked to NDMA exposure in previous animal research.[25,26] The study identified 11 cancer outcomes from the NHIS database, including those with high incidence rates. The cancer data included the following: primary malignant neoplasm of the liver (ICD-10 code C22); malignant neoplasm of the cecum, appendix, colon, and rectum (ICD-10 codes C18–20); malignant neoplasm of the stomach (ICD-10 code C16); malignant neoplasm of the bronchus and lung (ICD-10 code C34); malignant neoplasm of the kidney, excluding the renal pelvis (ICD-10 code C64); malignant neoplasm of the bladder (ICD-10 code C67); malignant neoplasm of the uterus, including the myometrium and cervix (ICD-10 codes C53–54); malignant neoplasm of the breast (ICD-10 code C50); malignant neoplasm of the thyroid gland (ICD-10 code C73); malignant neoplasm of the gallbladder and biliary tract (ICD-10 codes C23–24); and malignant neoplasm of the prostate (ICD-10 code C61). Patients with C-codes are required to pay only a small co-payment, amounting to 5% of the total treatment costs.[27]

Study Cohort

The study cohort included patients who were prescribed ranitidine between January 2009 and December 2011. Patients prescribed famotidine during the same period served as a comparison control group. Famotidine, like ranitidine, is an H2 receptor antagonist (H2RA) but does not contain NDMA, as confirmed by FDA testing. The duration of H2RA exposure for each patient was determined based on the intended prescription period recorded in the database. The study enrolled patients who had been using either ranitidine or famotidine for over one year during the specified timeframe. Ranitidine users with a cumulative dose exceeding 10,800 mg and famotidine users with a cumulative dose exceeding 14,400 mg were included. To standardize dosage comparisons between the two drugs, the defined daily dose (DDD) was calculated. The DDD represents the average maintenance dose per day for a drug when used for its primary indication in adults.[28]

Statistical Analysis

To address potential confounding caused by imbalances in baseline characteristics between the target and comparator cohorts, propensity score (PS) matching was employed. A comprehensive set of covariates was included to calculate the PSs, such as age, sex, race,

ethnicity, cohort entry timing (year and month), medication history, prior medical conditions, procedures, and the Charlson Comorbidity Index score during the year before the index date. Data on race and ethnicity were obtained from the databases. In the AmbEMR database, race was categorized as Asian, White, and African American, with provisions for missing data, while ethnicity was classified as Hispanic or Latino and Not Hispanic or Latino. These variables were incorporated into the analysis due to their potential influence on treatment decisions. Comparator cohorts were generated using 1:1 PS matching, applying a caliper of 0.2 standard deviations of the logit of the PS. The database-specific PSs were calculated using L1-regularized logistic regression optimized through 10-fold cross-validation.[29'30] Cox proportional hazards models were applied to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for each data source, utilizing the Cohort Method.[31]

Drug Profile of Ranitidine

Ranitidine

Ranitidine is part of a class of drugs known as histamine H2-receptor antagonists, which have antacid properties. It is commonly sold under the brand name Zantac, among others. Discovered in 1976 and introduced for commercial use in 1981, ranitidine is listed on the World Health Organization's List of Essential Medicines, recognizing it as one of the safest and most effective medicines necessary for a health system. It is available as a generic drug.

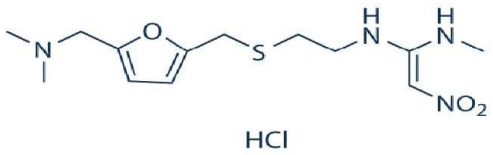

Fig. No. 2: Structure of Ranitidine Molecular Information.

- Molecular Formula: C13H22N4O3S
- Molecular Weight: 314.41 g/mol
- Physical Form: Solid
- Odor: Characteristic
- Taste: Bitter
- Bioavailability: 50% (when taken orally)
- Protein Binding: 15%
- Metabolism: Liver (via FMOs, including FMO3, and other enzymes)

- Onset of Action: 55–65 minutes (150 mg dose), 55–115 minutes (75 mg dose)
- Elimination Half-Life: 2–3 hours
- Excretion: 30–70% via the kidneys
- Boiling Point: 437.1 ± 45.0°C
- Melting Point: 134°C
- pKa: 8.2 and 2.7
- Solubility: Soluble in water.[9]

Mechanism of action

After eating, the hormone gastrin is released by cells in the stomach lining, stimulating the production of histamine. Histamine then binds to histamine H2 receptors, triggering the release of gastric acid. When ranitidine is administered, it works by reversibly binding to these H2 receptors on gastric parietal cells, preventing histamine from attaching. This inhibition reduces the secretion of gastric acid. Symptoms related to excess gastric acid can be relieved within 60 minutes of taking a single dose of ranitidine, with effects lasting between 4 to 10 hours, offering quick and effective relief from the condition.[10]

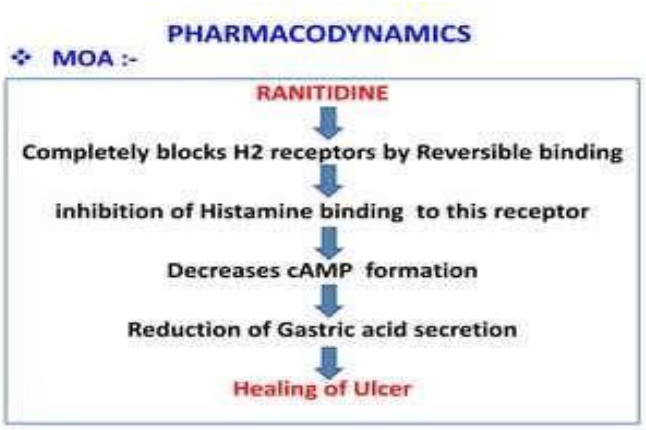

Fig. No. 3: Mechanism of action of ranitidine.

Uses

Ranitidine is used to treat stomach and intestinal ulcers and to prevent their recurrence after healing. It is also prescribed for conditions affecting the stomach and esophagus, such as erosive esophagitis, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome. Ranitidine works by reducing the amount of acid produced in the stomach, helping to alleviate symptoms like persistent cough, stomach pain, heartburn, and difficulty swallowing.[11]

Side Effects

Common side effects of ranitidine include constipation, diarrhea, nausea, dizziness, vomiting, stomach pain, headache, insomnia, reduced sex drive or difficulty reaching orgasm, and swollen or tender breasts.

Serious side effects can include coughing up green or yellow mucus, easy bruising or bleeding, unusual weakness, rapid or slow heart rate, vision problems, severe headaches with blistering, peeling, and red skin rashes, yellowing of the skin or eyes, dark urine, claycolored stools, and loss of appetite.[12]

Interactions

- Anticoagulants (blood thinners) such as warfarin (Coumadin)
- Triazolam (Halcion)
- Alcohol

Zantac Dosage

Marketed Preparation

Zantac is available in various forms, including tablets, syrup, effervescent tablets, and effervescent granules, all of which are taken orally. It is typically taken once a day at bedtime, or two to four times daily as prescribed. The medication can be taken with or without food. Be sure to follow the instructions on your prescription or the product label carefully. Effervescent tablets and granules should be dissolved in a full glass of water before consumption.[13]

Dosage Forms and Strength

Oral

- Treatment Dose: 150 mg taken orally twice a day or 300 mg once a day after the evening meal or at bedtime.
- Maintenance Dose: 150 mg taken orally once a day at bedtime.

Duration of Therapy: 8 weeks for treatment, up to 1 year for maintenance.

Fig. No. 4:- Ranitidine Tablet Parenteral (IM or IV).

- Usual Dose: 50 mg given intramuscularly (IM) or intravenously (IV) every 6 to 8 hours.
- Maximum Dose: 400 mg per day.
- Continuous IV Infusion:
- Usual Rate:6.25 mg/hour.
- IV bolus injections should be diluted to 2.5 mg/mL and injected at a rate of up to 4 mL/min.
- IV infusions should be diluted to a concentration of 0.5 mg/mL and infused at a rate of 5 to 7 mL/min (approximately 15 to 20 minutes).

Fig. No. 5: Ranitidine Injection.

Additional Information of Dosage Forms and Strengths

Oral dosing regimens (once or twice a day) have been shown to effectively inhibit gastric acid secretion.

Injectable forms do not require dilution when administered via IM injection, but intermittent IV bolus injections require dilution.

Most patients using oral formulations heal within 4 weeks. No safety data is available for treating uncomplicated duodenal ulcers beyond 8 weeks, and studies have not assessed the safety of oral maintenance therapy beyond 1 year.

Ranitidine Chemical Constituents

Ranitidine HCl is a white to pale yellow granular substance that is water-soluble, with a bitter taste and sulfur-like odor.

Zantac 150 Tablet - contains 168 mg of ranitidine HCl, equivalent to 150 mg of ranitidine. Inactive chemical constituents ingredients include FD&C Yellow No. 6 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Zantac 300 Tablet - contains 336 mg of ranitidine HCl, equivalent to 300 mg of ranitidine. Inactive chemical constituents ingredients include croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

Active Ingredient in Injectable Form

Ranitidine hydrochloride (HCl), the active ingredient in Zantac tablets, is a histamine H2receptor antagonist. Chemically, it is N[2-[[[5-[(dimethylamino)methyl]-2furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine, HCl.[14]

The Drug's Actual Truth

The elevated levels of NDMA found in ranitidine products were primarily due to the testing method used by Valisure, which involves heating the sample. The FDA stated in its October 2nd statement that this heating method is inappropriate for testing ranitidine, as itgenerates NDMA during the process. Instead, the FDA recommends using either liquid chromatography-tandem mass spectrometry (LC-MS) or liquid chromatography-highresolution mass spectrometry (LC-HRMS) for more accurate testing.

NDMA is an environmental contaminant found in drinking water, food (especially meats, dairy products, and vegetables), and various other sources. It is important to note that while NDMA is classified as a possible carcinogen, there are no direct health risks associated with the low levels of NDMA found in ranitidine products. Cancer would only be a concern from prolonged, high-dose exposure to NDMA.[19]

Ranitidine is typically recommended for short-term use in many situations. A 2016 study by Stanford University involving 10 healthy volunteers who took 150 mg of Zantac revealed that NDMA levels in their urine later exceeded 47,000 nanograms. The researchers noted that

most of the NDMA would have been broken down before reaching the urine, suggesting the total amount in the body could have been much higher. Another concern is the potential for ranitidine to enter the sewage system and contaminate drinking water if it breaks down into NDMA.

An independent lab in Almada, California, found preliminary evidence that ranitidinebased products can accumulate NDMA when exposed to high temperatures, which are often reached during shipping and storage. These issues arise after the manufacturer releases the product lot.[20]

Drug Profile of N-Nitrosodimethylamine (NDMA)

N-Nitrosodimethylamine (NDMA)

N-Nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN), is a semivolatile organic compound produced as a byproduct in various industrial processes. It is particularly associated with the production of unsymmetrical dimethylhydrazine (UDMH), a component of rocket fuel. NDMA is also generated during the manufacturing of goods in industries such as tanneries, pesticide plants, and rubber and tire factories. Additionally, it can be found in trace amounts in certain foods, especially those that are cooked, smoked, or cured.

NDMA is known for its toxic effects on the liver and other organs, and it is classified as a probable human carcinogen. It is also used in laboratory studies to induce cancer in rats for research purposes. Furthermore, the chlorination of drinking water and wastewater, a common process for water purification, can inadvertently produce NDMA.[15]

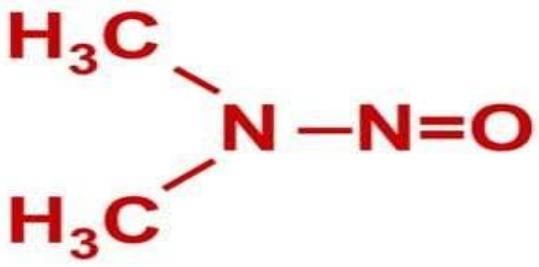

Fig. No. 6: Structure of N-Nitrosodimethylamine (NDMA).

Properties

NDMA is a yellow, oily liquid that has a faint, distinctive odor and a sweet taste. It is a byproduct or waste product generated from several industrial processes.[16]

1. Chemical formula:C2H6N2O
2. Molar mass: 74.083 g·
3. mol−1 Appearance: Yellow, oily liquid
4. Odor: faint, characteristic
5. Density: 1.005 g/ml
6. Boiling point: 153.1 °C; 307.5 °F; 426.2 K
7. Solubility: in water290 mg/ml (at 20 °C) log P: −0.496 8. Vapor pressure:700 Pa (at 20 °C) Refractive index (nD):1.437.

Uses

Used as an antioxidant, as an additive for lubricants and as a softener of copolymers.

Adverse Effects

1. Acute Effects

Acute exposure to N-nitrosodimethylamine (NDMA) can cause liver damage in humans, with symptoms such as nausea, vomiting, headaches, dizziness, and general discomfort. In animals, acute exposure through inhalation or ingestion has led to hematological issues and severe liver damage, including hemorrhagic necrosis. Studies in rats, mice, and hamsters have shown that NDMA poses a high to extreme acute toxicity risk from both inhalation and oral exposure.

2. Chronic Effects

Long-term exposure to NDMA in humans can lead to liver damage, characterized by swelling, low platelet counts, and a risk of jaundice. Chronic oral exposure has also caused severe liver damage in various animal species.[17]

Cancer Risk

Human studies on the cancer risk of N-nitrosodimethylamine (NDMA) are limited, as exposure to nitrosamines typically occurs through contact with mixtures of these compounds. However, NDMA has been shown to be carcinogenic in several animal species, causing tumors in various organs through different routes of exposure. Inhalation of NDMA has led to increased incidences of liver, kidney, and lung tumors in rats and mice. Additionally, liver tumors have been observed in rats, mice, and hamsters exposed to NDMA orally.

Due to the potential cancer risk, regulatory agencies, including the FDA, have been investigating the effects of ranitidine. On September 13, 2019, the FDA revealed that preliminary tests had detected low levels of NDMA in ranitidine, a widely used heartburn medication. This prompted drug companies, including Novartis (through its generic division, Sandoz) and Apotex, to recall all their generic ranitidine products sold in the U.S. The recall followed a report from a Connecticut-based online pharmacy that had detected NDMA in multiple ranitidine products under certain test conditions.

As of September 27, 2019, two manufacturers had recalled ranitidine, also known by the brand name Zantac, due to concerns over NDMA contamination. NDMA is considered a probable human carcinogen and has been shown to cause tumors and deaths in animals in laboratory tests. While the FDA stated that NDMA is generally safe in small doses and noted that the levels found in ranitidine were only slightly above those found in common foods, the exact cause of the NDMA contamination in ranitidine remains unclear. It is possible that NDMA is formed during the drug's synthesis using dimethylamine, or it may result from the breakdown of ranitidine during storage. Understanding the source of contamination is critical for ensuring future formulations are free of NDMA.[18]

Misconceptions Raised and Ban of the Drug

The issue first emerged in June 2019 when the US online pharmacy Valisure alerted regulators that their testing had revealed that ranitidine samples contained levels of the cancer-causing contaminant nitrosamine (N-nitrosodimethylamine, or NDMA) exceeding permissible limits. On September 13, 2019, Valisure filed a detailed citizen petition with the FDA, highlighting the presence of “alarmingly high levels of NDMA” in every lot tested, spanning multiple manufacturers and dosage forms of ranitidine.[22]

According to the petition, Valisure detected over 3 million nanograms of NDMA per tablet, well above the FDA's daily allowable intake limit of 96 nanograms. The FDA has stated that it has not received any reports of adverse reactions or incidents related to the NDMA found in ranitidine from other authorities. Meanwhile, the Drug Controller of India (DCGI) has instructed state drug authorities to ensure that the safety of ranitidine is thoroughly confirmed, despite many global regulators having already banned its sale and production. The FDA has recommended that companies conduct laboratory testing to assess NDMA levels.[23]

CONCLUSION

The ban on Ranitidine in India is a significant step taken to safeguard public health. It reflects the government and regulatory bodies' commitment to ensuring drug safety and addressing potential risks associated with medicines. While Ranitidine was once widely used for the treatment of acidity, ulcers, and related conditions, its potential contamination with harmful substances like N-Nitrosodimethylamine (NDMA) raised concerns about its long-term safety. Patients are encouraged to consult healthcare professionals for safer alternatives and be vigilant about the medicines they consume.

NDMA is a probable human carcinogen (a substance that can cause cancer) identified during stability testing of Ranitidine. Its levels were found to increase over time or under certain storage conditions, leading to potential health risks. Regulatory authorities like the US FDA and European Medicines Agency (EMA) flagged Ranitidine for investigation. Several countries recalled Ranitidine-containing products due to NDMA contamination, prompting India to take similar measures. The Central Drugs Standard Control Organization (CDSCO) reviewed safety data and recommended the ban as a preventive action to mitigate health risks for millions of users in India.Safer and equally effective alternatives, such as proton pump inhibitors (e.g., omeprazole, pantoprazole), were already available, making the transition for patients more feasible.

Given the widespread use of Ranitidine in India, the ban aimed to prevent long-term exposure to potentially carcinogenic substances, reinforcing trust in the regulatory system.This decision underscores the importance of stringent drug monitoring and prioritizing patient safety over commercial interests.

Global Investigation Report[21]

Table No. 1: Global Investigation Report.

Region	Regulatory Authority	Action Taken	Outcome
India	Central Drugs Standard Control Organization (CDSCO)	Ranitidine was banned in India (April 2020) by CDSCO due to NDMA contamination concerns, suspending its manufacture, sale, and distribution.	Ranitidine was banned in India in 2020 due to NDMA contamination, leading to its suspension and use of safer alternatives.
United States	Food and Drug Administration (FDA)	FDA alerted the public about NDMA contamination in	Several manufacturers voluntarily recalled ranitidine-based

		ranitidine products in 2019.	medications. Patients advised to seek alternatives.
European Union	European Medicines Agency (EMA)	EMA conducted a thorough review and suspended ranitidine use due to NDMA concerns in September 2019.	Ranitidine use was suspended, affecting availability in EU member states.
Canada	Health Canada	Regulatory action taken against ranitidine due to NDMA contamination.	Ranitidine-containing products were banned or restricted.
Bangladesh	Directorate General of Drug Administration (DGDA)	Regulatory action against ranitidine due to NDMA concerns.	Ranitidine-containing products were banned or restricted.
Egypt	Egyptian Drug Authority (EDA)	Banned or restricted ranitidine-containing products due to NDMA contamination.	Ranitidine-containing products were banned or restricted, emphasizing safer alternatives

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