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Administrative Notice
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To: Commissioners of Prefectural Health Departments (Bureaus)

Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Results of the Health Effect Assessment of the Use of Ranitidine Hydrochloride Products or Nizatidine Products in Which N-dimethylnitrosamine Was Detected

Regarding ranitidine hydrochloride products, it was announced in September last year that very low levels of N-dimethylnitrosamine (hereinafter referred to as "NDMA"), a carcinogenic substance, had been detected overseas. Subsequent to the announcement, it was found that there was the potential in Japan as well for NDMA to be contained in ranitidine products at levels above the acceptable limit. This finding among others led to voluntary recalls of all ranitidine hydrochloride products marketed in Japan. In addition, NDMA has been detected at levels above the acceptable limit in certain lots of products of nizatidine, which has a similar chemical structure to ranitidine, and the affected lots were voluntarily recalled.

Recently, we have assessed the health effects of these drug products on people who have used them in the past, and we reported the results to the 5th fiscal year 2020 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council. Commissioners of Prefectural Health Departments are requested to notify medical institutions and pharmacies under their supervision of the report as quoted below for their reference when they receive inquiries from patients regarding the issue.

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1. All ranitidine hydrochloride products marketed in Japan have been volunta+rily recalled and are no longer distributed in Japan.

   In addition, the lots of nizatidine products in which NDMA was detected at levels above the acceptable limit have been voluntarily recalled and are no longer distributed. At present, nizatidine products currently marketed in Japan (including OTC drugs) are properly controlled to keep the levels of NDMA below the acceptable limit by marketing authorization holders (MAHs).

* 0.32 ppm (calculated based on the acceptable daily intake limit for NDMA at 0.0959 μg/day)

2. Assessment results on the theoretical risk for cancer due to use of ranitidine hydrochloride or nizatidine products in which NDMA was detected at levels above the acceptable limit are shown in the table below.

   With reference to the guideline*[1], the assessment was conducted in two different standard periods of use: Short-term use (initial treatment) and long-term use (maintenance therapy). The highest value of NDMA content in a drug product of all the analysis results was used for the assessment of short-term use for less than 1 year because a single lot may be used in such situations. On the other hand, for the assessment of long-term use for 1 year or longer, the average of the analysis results of each lot calculated for each of the MAHs individual products was determined and the highest average value was used, assuming that multiple lots would be used in such situations. Consequently, the NDMA content in a product, as the prerequisite for assessment, differs between short-term and long-term use assumed.

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Types of drugs	Assumed situation for use[*2, *3]	Theoretical lifetime excess risk for cancer[*3]
Ranitidine hydrochloride (oral drug products)	Ranitidine 300 mg daily for 8 weeks	Less than "an excess risk of approximately 1 in 80 000 persons developing cancer," which is the risk when taking ranitidine 300 mg daily for 1 year
	Ranitidine 300 mg daily for 2 years	An excess risk of approximately 1 in 200 000 persons developing cancer
Ranitidine hydrochloride (injections)	Ranitidine 200 mg daily for 7 days	Less than "an excess risk of approximately 1 in 3 million persons developing cancer," which is the risk when taking ranitidine 200 mg daily for 1 year
Nizatidine (oral drug products)	Nizatidine 300 mg daily for 8 weeks	Less than an excess risk of "approximately 1 in 3.8 million persons developing cancer," which is the risk when taking nizatidine 300 mg daily for 1 year
	Nizatidine 300 mg daily for 2 years	An excess risk of approximately 1 in 5.6 million persons developing cancer

[*1] Evidence-based Clinical Practice Guidelines for Peptic Ulcer 2015 (Revised 2nd Edition) (compiled by The Japanese Society of Gastroenterology)

[*2] Using rodent carcinogenicity data (TD_{50} values), the probability was calculated for additional humans to develop any type of cancer in their lifetime (assuming 70 years) due to exposure to NDMA during assumed use.

[*3] Decided based on the idea that the risk of cancer increases in proportion to the duration of exposure. Since quantitative assessment is difficult for short-term use of less than 1 year, the decision was made compared to the risk with daily use for 1 year as "less than the risk with daily use for 1 year," although theoretically the risks with ranitidine (oral drug products) 300 mg daily for 8 weeks, with ranitidine (injections) 200 mg daily for 7 days, and with

nizatidine (oral products) 300 mg daily for 8 weeks are calculated to be approximately an excess risk of 1 in 500 000 persons, 1 in 150 million persons, and 1 in 25 million persons developing cancer, respectively.

The Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (ICH M7 guideline) states that the risk of “approximately 1 additional cancer per 100,000 persons” is acceptable, and most of the above-mentioned assessment results are below this limit. The risk with ranitidine 300 mg (oral drug products) daily for 8 weeks is considered to be “less than “an excess risk of 1 in approximately 80 000 persons developing cancer” which is the risk of taking the drug product (ranitidine 300 mg (oral)) daily for 1 year. This is a conservative assessment due to the difficulty of quantitative assessment in short-term use. Under any situations for use assessed, the risks are considered to be contained within acceptable limits of the ICH M7 guideline.

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[References]

・Materials 2-1 of the 5th FY 2020 Subcommittee on Drug Safety of the Committee on Drug Safety

https://www.mhlw.go.jp/content/11120000/000651728.pdf (only in Japanese except for part of Appendix 3 posted together in English)