**NOTIFICATION TO THE CHMP SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC**

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by the European Commission:

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| Product Name(s) in the Referring Member State, if applicable | Ranitidine |
| Active substance(s)<br>*Please clarify name(s)* | Ranitidine |
| Pharmaceutical form(s)<br>*If all pharmaceutical forms are included, state "All".*<br>*If not all pharmaceutical forms are included, please specify the one included.* | All |
| Strength(s)<br>*If all strengths are included, state "All".*<br>*If not all strengths are included, please specify the one included.* | All |
| Route(s) of Administration<br>*If all routes of administration are included, state "All".*<br>*If not all routes of administration are included, please specify the ones included.* | All |
| Applicant(s)/Marketing Authorisation Holder(s) in the referring Member State | Several |

Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H2-receptors on parietal cells in the stomach. It is indicated for the management of peptic ulceration, Gastroesophageal Reflux Disease (GERD), reflux oesophagitis, Zollinger-Ellison syndrome, chronic episodic dyspepsia, peptic ulcer hemorrhage, prophylaxis of stress ulceration, Mendelsons syndrome, duodenal ulcers, benign gastric ulcers, post-operative ulcer, symptomatic relief of heart burn, dyspepsia (acid indigestion), hyperacidity, and prevention of symptoms associated with consuming food and drink. Ranitidine is available for oral and parenteral administration.

The EU authorities were notified of the results of a preliminary laboratory analysis of ranitidine showing the presence of N-Nitrosodimethylamine (NDMA). The results on a limited sample of products showed that for the majority of both ranitidine APIs and finished products, NDMA was above the acceptable intake established during the referral procedure under Article 31 of Directive 2001/83/EC for sartans with a tetrazole ring (considering the maximum daily dose authorised in the EU, and long-term use in a 50 kg adult). Following extensive validation of the analytical method, the presence of NDMA in ranitidine finished products was confirmed.

NDMA is a genotoxic and carcinogenic agent in animals and it is classified as a probable human carcinogen by IARC (International Agency for Research on Cancer, WHO).
From the preliminary investigations the root cause of the presence of NDMA is still unclear. Based on the ranitidine structure, NDMA might potentially be generated by degradation of the API in presence of nitrites under certain conditions. In the manufacturing processes nitrite could possibly be introduced in the API during synthesis, or in the finished product through excipients or through other still unknown mechanisms (the nitro group in ranitidine may generate nitrite).

According to preliminary results for NDMA levels in a random selection of ranitidine API batched and finished products available in the EU, the levels of NDMA detected raise concerns according to the principles of ICH-M7.

In addition, in vitro studies were performed with different pH solutions of ranitidine with and without nitrite to evaluate if similar pH conditions as in vivo conditions would lead to formation of NDMA. Although the nitrite levels used were far above those usually present in human stomach, the results seem to indicate that NDMA could be formed from ranitidine at acidic pH in the presence of nitrite and therefore suggest a plausible path for NDMA formation under certain conditions.

These test conditions however do not reflect the NDMA levels that would be generated in patients taking ranitidine with natural ingestion of nitrite and their relevance in humans is currently not known. These results should be interpreted with caution as NDMA can also be formed from ranitidine during analytical procedures which use high temperatures.

Overall, in view of preliminary results showing the presence of NDMA in some batches of drug substance and drug product and the preliminary findings that NDMA could be generated under certain conditions when dimethylamine (DMA) released from ranitidine is exposed to a source of nitrite (e.g. sodium nitrite), it is necessary to evaluate the relevance of these findings, the potential root causes and their impact on the benefit–risk balance of the medicinal products containing ranitidine.

The following aspects should be considered:

- the potential root causes that may lead to the presence of NDMA (or other nitrosamines) in the active substance of the medicinal product and/or medicinal product-containing ranitidine
- the potential formation of nitrosamines from ranitidine in vivo
- the suitability of the manufacturing processes and the in-process controls, storage conditions, the analytical methods used and the specifications of the active substance and finished products;
- should the risk of patients' exposure to NDMA (or other nitrosamines) be confirmed, potential subsequent measures may be implemented including further guidance for healthcare professionals and patients.

It should also be considered whether any findings from this review could be of relevance for other medicinal products.

In view of the above and the necessity to conduct an EU assessment for any potential action to be taken at EU level, the European Commission considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC on the issues raised above and their impact on public health and the benefit–risk balance of the concerned medicinal products.

In particular, taking into account the conclusions from Article 31 of Directive 2001/83/EC for sartans with a tetrazole ring, the European Commission requests the Agency to give its opinion as soon as possible and at the latest by February 2020 on whether marketing authorisations of these products should be maintained, varied, suspended or revoked. The CHMP is asked to consider the principles set out in the sartans referral in carrying out the assessment for ranitidine.

[redacted]

12/9/2019

Date

[redacted]

Directorate-General Health and Food Safety
European Commission