19 September 2019
EMA/CHMP/506572/2019

CHMP List of questions

To be addressed by the marketing authorisation holders for ranitidine-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1491

INN/active substance: ranitidine

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1. Background

Following information indicating presence of nitrosamine in ranitidine containing medicinal products, tests performed in a random selection of ranitidine API batches and finished products available in the EU have shown levels of N-Nitrosodimethylamine (NDMA) which raise concerns according to the principles of the ICH M7 guideline.

In addition, in-vitro studies with different pH solutions of ranitidine with and without nitrite to determine whether gastric pH conditions could lead to formation of NDMA indicated that NDMA could be formed from ranitidine at acidic pH in the presence of (high levels of) nitrite and therefore suggest a possible path for NDMA in-vivo formation under certain conditions.

In view of the analytical results presented so far, it appears that NDMA can also be formed from ranitidine during certain analytical procedures, especially those using high temperatures.

Overall preliminary results show the presence of NDMA in some batches of drug substance and drug product and preliminary findings indicate 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).

The European Commission triggered on 12 September 2019 a referral procedure under Article 31 of Directive 2001/83/EC to evaluate the relevance of these findings, the potential root causes and their impact on the benefit-risk balance of medicinal products containing ranitidine.

2. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Quality

1. Each MAH should assess the potential for NDMA formation from representative API and finished product batches following stress testing under conditions described in ICH Q1A and ICH Q1B guidelines. This may include e.g. testing in acidic/basic/oxidative solutions (including high temperature) and in the solid phase at high temperature and humidity among other conditions.
2. Each MAH is requested to test for NDMA content in its batches of their finished products containing ranitidine as well as the batches of API used in their finished products released in the EU/EEA market (using published validated analytical methods for ranitidine, e.g. the method published by FDA, see https://www.fda.gov/media/130801/download). Details and validation status of the analytical method(s) used should be provided. The test results (in ppm calculated on API) should be provided using the annexed Excel template for all batches tested (including negative results), with information on API and corresponding finished product, if available. API tested should include batches at or approaching retest dates and finished product tested should include batches at or approaching expiry dates. Information should be provided on expiry dates and retest dates of batches tested.
3. Each MAH should comment on any variability of the contamination in an adequate number of batches tested, e.g. in view of any process parameters that may specifically impact on the formation of NDMA or potential differences in process, equipment, analytical methods or others, such as storage conditions/shelf life.

4. Nitrosamines can be generated when secondary or tertiary amines are present at the same time as nitrosating agents (abbreviated to NOx, commonly from sodium nitrite). Each MAH should comment on the likely root causes of nitrosamine presence in ranitidine. In case the manufacturing process is considered to be at risk of forming other nitrosamines than NDMA, test results should be provided as well (as per Question 2 above)

5. Each MAH should provide details of any proposed corrective and preventive actions to reduce the risk as much as possible that the API or finished product contains NDMA (or any other nitrosamine). Please comment on potential foreseen changes to manufacturing process, in-process controls, specifications and related analytical methods for the API and their validation.

In-vitro/in-vivo aspects

6. Each MAH should submit all relevant data on the carcinogenic potential of ranitidine use. This should include in-vitro incubations with ranitidine and its metabolites and in-vivo studies (non-clinical and clinical) where generation of NDMA and/or dimethylamine has been investigated (e.g. in simulated gastric conditions or hepatocytes). A further discussion of the possible reasons for the findings, including a description of the plausible pathway(s) involved in the endogenous formation of NDMA from ranitidine within the human body, is also requested. This should include an appraisal of the potential for NDMA and dimethylamine generation following absorption or within the gastro-intestinal tract by chemical degradation, enzymatic conversion or formation by gastro-intestinal microflora.

7. Please provide a critical appraisal of the most recent data on the carcinogenic potential of ranitidine use. The analysis should include a review of the literature namely a discussion on the Zeng et al. (2016) [1] publication.

8. Based on the risk of NDMA presence in your medicinal product(s) and/or the potential endogenous formation above, a discussion on the impact on the benefit-risk balance and your plans for actions should be provided, as applicable, taking into account the importance to obtain human data, specifically to look into excretion, and complement those results with in-vitro testing.

General aspects

9. Concerning your ranitidine -containing medicinal product(s) please provide in the annexed table (Annex 2):
   Information on type of marketing authorisation, marketing and legal status, whether currently marketed or not, and an overview of the approved indication(s). Figures on sales and patient exposure by product, member state, indication and age. Data on the use in clinical practice including information on dose, duration of treatment and concomitant treatment (characterisation of users, prescriptions).

1. *Zeng et al., Carcinogenesis, 2016, Vol. 37, No. 6, 625–634*

Annexes

1) Excel template for results

TEMPLATE
Ranitidine sampling ar

2) Product overview

Product name	Type of marketing authorisation	Marketing and legal status	Indications[1]	Pharmaceutical forms and strengths	Sales figures	Estimated patient exposure[2]	Doses (as approved and used in clinical practice)	Treatment duration (as approved and used in clinical practice)

[1]. MAH should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication
[2]. Expressed in patient years and stratified by Member State, by indication and by age (e.g. <12, 12-18 and adults). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.