Annex II

Scientific conclusions

Scientific conclusions

In July 2019, findings from a private laboratory in the United States (US) indicated that ranitidine can generate NDMA as a decomposition product. In August 2019, preliminary results in a random selection and testing by official medicinal control laboratories (OMCLs) of ranitidine API batches and finished products available in the EU showed levels of NDMA in a range that raised 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 to the *in vivo* conditions would lead to the 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. Based on the analytical results available at the start of the referral procedure, it appeared that NDMA can also be formed from ranitidine during certain analytical procedures, especially those using high temperatures.

Overall, it was considered possible that NDMA could be generated under certain conditions when DMA released from ranitidine is exposed to a source of nitrite (e.g. sodium nitrite).

The European Commission considered it 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.

In view of the above, 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 and take any subsequent action as required.

Overall summary of the scientific evaluation

NDMA is a potent mutagenic carcinogen in a number of different animal species and on the basis of animal data, NDMA is classified by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans". Despite of the fact that the impact of NDMA on human health is currently only extrapolated from animal studies, it is prudent to assume that effects seen in animals may also occur in humans.

Almost all batches of ranitidine API and drug products that have been tested for NDMA, contain NDMA above 0.16 ppm, which is based on an acceptable intake of 96 ng/day for a lifetime and a maximum daily ranitidine dose of 600 mg for a lifetime. Necessary information related to the presence of NDMA in the final product, including formation of NDMA as a degradation product and/or metabolite, is still lacking. The risk of contamination with potential carcinogenic nitrosamines, especially with NDMA, above the acceptable daily intake, is unresolved.

Based on the review of all available data on safety and efficacy and additional information received during the oral explanations, the CHMP considers that the risk of presence of NDMA cannot be adequately addressed at this stage, and therefore avoiding the use of ranitidine containing products until the above uncertainties are addressed is the only acceptable risk minimisation measure. The CHMP concluded that the benefit-risk balance of medicinal products containing ranitidine is negative in view of the uncertainties on the root causes for the presence of NDMA in the active substance and drug products, and in view of the fact that the risk of endogenous formation of NDMA following administration of ranitidine to patients cannot be excluded at this stage.

These elements related to the formation of NDMA as a degradation product and/or metabolite and the potential for endogenous formation need to be answered. As a consequence, the CHMP has recommended to suspend all marketing authorisations for ranitidine-containing medicinal products. The CHMP noted that treatment alternatives for ranitidine are available.

In order to lift the suspension of the marketing authorisation (MA), all the following conditions must be fulfilled:

- the MAH(s) shall investigate the potential endogenous formation and demonstrate that it supports a positive benefit/risk balance,
- introduce in the MA dossier an adequate limit to control presence of nitrosamines and
- to put in place a control strategy.
- The limit at release will need to be based on the maximum daily dose of ranitidine free base taking into account the route of administration in accordance with the ICH M7(R1) guideline, with a maximum daily intake of NDMA of 96 ng/day. This limit at release should take into account any increase in NDMA levels observed during stability studies. The MAH(s) shall also provide batch data for the drug products to demonstrate that the degradation of the drug substance is controlled throughout shelf-life.

The ICH M7(R1) guideline sets out principles for determining limits for mutagenic / DNA-reactive impurities. N-nitrosamines belong to a "cohort of concern" compounds in this guideline. Based on the principles in ICH M7, a daily exposure to NDMA of 96 ng was previously set as Acceptable Intake (AI), which is associated with an additional tumour risk of 10-5. Assuming a maximum daily dose of 600 mg for a lifetime (or in excess of 10 years) this AI leads to a limit of 0.16 ppm in ranitidine containing medicinal products.

A limit based on the AI would be toxicologically justifiable since the excess tumour risk would not exceed 10-5 (or 1:100,000 patients). Considering that NDMA is a degradant, lower limits are unlikely to be achievable in the case of ranitidine. This is different from case of the sartans where a change of the methods of synthesis could sufficiently circumvent the formation of N-nitrosamines.

This limit is based on an exposure throughout life. The 'Less-than-Lifetime' (LTL) approach that would include a correction factor leading to a higher limit is not acceptable in view of the risks of NDMA, the unclear degradation profile, the benefits of ranitidine and the potential repeated use throughout life or chronic use.

The MAH(s) should also put in place a control strategy which should include current and prospective measures to minimise the risk of generation/contamination with any nitrosamine (e.g. change of manufacturing process, introduction of appropriate specifications and development of appropriate methods, measures on the premise and equipment, such as cleaning procedures, environmental monitoring) and control any future change that may impact on this risk (e.g. change of supplier, change of manufacturer process, change of packaging).

As part of the control strategy, the MAH(s) should introduce every necessary change to control the risk of presence of N-nitrosamines and to minimise as much as possible their presence below the limit based on the acceptable intake.

Re-examination procedure

Following the adoption of the CHMP Opinion during the April 2020 PRAC meeting, one MAH (S.A.L.F.) expressed its disagreement with the initial CHMP Opinion, and subsequently to the request for re-examination, grounds for re-examination have been submitted by S.A.L.F. The CHMP confirmed it had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure. Notwithstanding this, and given the detailed grounds provided by the MAH, the CHMP carried out a new assessment of the available data in the context of the re-examination.

CHMP conclusions on grounds for re-examination

Clinical aspects

It is scientifically plausible that the underlying disease increases the risk for gastric and pancreatic cancers in patients treated with H2-receptor antagonists. The impact of NDMA on human health is therefore, extrapolated from animal studies. DNA damage mechanisms documented in animal studies are also relevant in humans, it is plausible to assume that effects seen in animals may also occur in humans after exposure to sufficiently large amounts of this nitrosamine. Besides exposure through ranitidine when containing NDMA as impurity, it cannot be excluded that additional exposure to NDMA can be due to endogenous formation of NDMA from ranitidine. These should be seen as additional risk factors adding to the total tumour risk associated with nitrosamine background exposure. However, any potential cancer risk due to NDMA exposure associated with ranitidine use is of a low level and will probably not be detected with conventional animal studies or epidemiological studies considering the latency of cancer onset and that any potential cancer risk due to NDMA exposure associated with ranitidine use is of a low level compared to the background cancer risk over lifetime. Therefore, whilst epidemiological or clinical trial data did not indicate an increased risk of cancer in humans after the use of ranitidine, a theoretical risk cannot be excluded.

Less-than-Lifetime (LTL) approach

In view of the MAH's proposal to use the LTL approach considering the duration of use for Ranitidina S.A.L.F, the CHMP reconfirmed its position that this approach is only accepted for N-nitrosamine contaminations in exceptional circumstances. The CHMP did not identify such exceptional circumstances in this case. It is also noted that there are uncertainties on potential endogenous formation of NDMA from intake of ranitidine, which prevent the use of the LTL approach.

In agreement with the CHMP's previous opinion, a limit for NDMA in ranitidine based on the maximum daily dose, assuming exposure throughout life is considered scientifically robust. Where the duration of use is shorter, this would further mitigate the actual risks for the patients, but not allow for setting higher limits. The CHMP also noted that for a single dose administration, considering an NDMA limit of 96 ng/day and a 50 mg single dose used in the setting of a single use application prior to surgery for prevention of Mendelson's syndrome the limit would be 1.92 ppm NDMA.

NDMA is not only present in ranitidine finished products as an impurity but also appears to increase over time as a consequence of degradation of the active substance over shelf-life of the finished product. In addition, the possibility that endogenous formation of NDMA arises from ranitidine administration cannot be excluded. Assessment of the clinical safety of ranitidine products therefore cannot be fully elucidated and further investigations into endogenous formation of NDMA should be carried out.

For the above reasons the CHMP considered that the MAH's proposal to use the LTL approach cannot be accepted for the reasons explained in the paragraphs above, and that any limits – once adequate data on degradation are available – should be guided by lifetime exposure, i.e. 96 ng NDMA /day.

Use of parenteral ranitidine in prevention of Mendelson syndrome only

The MAH proposed as an alternative of defining NDMA limit for their products based on LTL approach, to limit the current therapeutic indications only to the anaesthesia premedication for those patients who risk developing an acid aspiration syndrome (Mendelson syndrome). The MAH argued that since it is a single administration, the nitrosamine content is irrelevant.

In this re-examination procedure, the only risk minimisation measure identified by the MAH to reduce exposure with NDMA was limiting the use of ranitidine to a single administration for anaesthesia premedication to those patients who risk developing an acid aspiration syndrome (Mendelson

syndrome). As mentioned above, the proposed measure would reduce the exposure but not the risk for the patients exposed. The CHMP also did not identify exceptional circumstances for this indication that would justify the LTL approach in this setting for the same reasons discussed above.

The CHMP considered that there are too many uncertainties on the risk of endogenous NDMA formation from ranitidine and degradation over time from the active substance leading to NDMA. The CHMP considered that these risks outweigh the benefits, therefore the CHMP confirmed its initial position that the benefit-risk balance in all ranitidine formulations (including parenteral) is currently negative.

The CHMP however acknowledged the MAH's argument that the risk might be lower for the use of ranitidine when given parenterally as a single low dose administration. The rationale for this, is that it could be plausible that with the lower dose administered (and as a single use), there is a lower relevance of potential NDMA endogenous formation in kidney in this clinical setting due to the lower exposure following single use administration. It can therefore not be excluded that the potential risk with single use is very small or negligible.

The CHMP agreed to take this element in the requirements to establish a positive benefit-risk balance and to adapt the expected data to be submitted in order to justify a positive benefit-risk of these products. Hence the 1st condition for lifting the suspension of ranitidine-containing medicinal products for single parenteral use only requests the MAH to discuss the relevance of endogenous NDMA formation based for these products as follows:

1. In order to support a positive benefit-risk balance of these products the MAH should discuss the relevance of endogenous NDMA formation based on e.g. data on endogenous formation of NDMA in humans from ranitidine, additional experimental data (*in vitro*/*in vivo*) or literature information.

The other conditions requested in the initial phase of this procedure are maintained for all products:

2. "A limit for NDMA should be set in the release specification of the medicinal product. This limit should take into account any increase in NDMA levels observed during stability studies. The limit at the end of shelf life should be based on the maximum daily dose of Ranitidine free base taking into account the route of administration in accordance with ICH M7(R1), with a maximum daily intake of NDMA of 96 ng/day.
3. Compliance with the limit for NDMA up to the end of shelf-life of the medicinal product should be demonstrated through appropriate data from batches of the medicinal product.
4. The MAH should implement a control strategy regarding N-nitrosamines for ranitidine containing medicinal products."

For all other cases (oral formulations or other indications for parenteral formulations), the 1st condition for lifting a suspension agreed in the initial phase of the referral should apply:

1. "The MAH should submit quantitative data on the endogenous formation of NDMA in humans from ranitidine and demonstrate whether the results support a positive benefit-risk balance of the product."

Final benefit-risk balance

On 3 June 2020 one MAH (S.A.L.F.) submitted detailed grounds for re-examination of the initial CHMP opinion.

The CHMP, having reviewed the grounds from the MAH and the available clinical safety data confirmed its previous position that there is no evidence of a causal association between ranitidine therapy and the development of cancer in patients and that therefore the corresponding statement does not need to be changed. However, any potential cancer risk due to NDMA exposure associated with ranitidine

use is of a low level and will probably not be detected with conventional animal studies or epidemiological studies. Whilst epidemiological or clinical trial data did not indicate an increased risk of cancer in humans after the use of ranitidine, a theoretical risk cannot be excluded.

Based on all the available data and having carefully assessed the grounds for re-examination, the CHMP confirmed that the LTL approach is not appropriate to justify a higher amount of NDMA in ranitidine-containing parenteral formulations.

No other risk minimisation measure than limiting the use as a single administration for anaesthesia premedication to those patients who risk developing an acid aspiration syndrome (Mendelson syndrome) was identified by the MAH. However, whilst a shorter duration of use would further mitigate the actual risks for the patients, this cannot allow for setting higher limits.

Therefore, in view of the uncertainties on the risk of endogenous NDMA formation from ranitidine and degradation over time from the active substance leading to NDMA, the CHMP considered that the risks related to the presence of NDMA in ranitidine containing products outweighs the benefits. Consequently, the CHMP considers that the benefit/risk balance for all medicinal products containing ranitidine is negative.

The CHMP considered that for single use IV formulations, it could be plausible that with the lower dose administered (and as a single use), there is a lower relevance of potential NDMA endogenous formation in kidney due to the lower exposure following single use administration. The CHMP revised the conditions for lifting the suspension of the MAs to take this element into account for these specific medicinal products.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing ranitidine.
- Tests carried out by Marketing Authorisation Holders, API manufacturers, Official Medicines Control Laboratories and international competent authorities showed that NDMA, classified by the IARC as "probably carcinogenic to humans" (Class 2A carcinogen), was found in almost all batches of ranitidine drug substances and medicinal products tested above the acceptable level based on the current principles established in ICH M7(R1).
- The CHMP reviewed all available data to evaluate the potential root causes that may lead to the presence of NDMA in the ranitidine drug substance and medicinal product. The CHMP also considered the grounds submitted by one MAH (S.A.L.F) as basis for their request for re-examination of the CHMP opinion.
- The CHMP concluded that NDMA is not only present in ranitidine-containing medicinal products as an impurity that may form during the manufacturing process, but also due to degradation of ranitidine as a drug substance. The degradation of ranitidine in drug substance and medicinal product is currently insufficiently characterised.
- In addition, the CHMP concluded that the risk of endogenous formation of NDMA following administration of ranitidine cannot be excluded at this stage and that further investigation should be carried out.
- While epidemiological or clinical trial data did not indicate an increased risk of cancer in humans after the use of ranitidine, a risk cannot be excluded, as the currently available data may not be able to detect such a risk.

- The extent of formation of NDMA especially due to degradation of the drug substance and the potential endogenous formation raise serious concerns related to the safety of ranitidine-containing medicinal products. In view of these uncertainties on the presence of NDMA in the medicinal product, the risk of *in vivo* formation as well as its extent, the CHMP did not identify risk minimisation measures other than avoiding its use that could minimise the risk to an acceptable level at this stage. Therefore, the CHMP considered that the risks related to the presence of NDMA in ranitidine containing products outweighs the benefits. Furthermore, due to the above concerns, the CHMP did not support using a less -than-lifetime (LTL) approach for setting future NDMA limits for ranitidine.
- The CHMP considered that for single use parenteral formulations, it could be plausible that there is a lower relevance of potential NDMA endogenous formation in kidney due to the lower exposure following single use administration.

CHMP opinion

The CHMP, as a consequence, considers that the risk-benefit balance of ranitidine-containing medicinal products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CHMP recommends the suspension of the marketing authorisations for ranitidine-containing medicinal products.

For the suspension of ranitidine-containing medicinal products to be lifted, the marketing authorisation holder(s) shall submit:

<u>For ranitidine containing medicinal products for single use:</u>

1. In order to support a positive benefit-risk balance of these products the MAH should discuss the relevance of endogenous NDMA formation based on e.g. data on endogenous formation of NDMA in humans from ranitidine, additional experimental data (in vitro/in vivo) or literature information.
2. A limit for NDMA should be set in the release specification of the medicinal product. This limit should take into account any increase in NDMA levels observed during stability studies. The limit at the end of shelf life should be based on the maximum daily dose of Ranitidine free base taking into account the route of administration in accordance with ICH M7(R1), with a maximum daily intake of NDMA of 96 ng/day.
3. Compliance with the limit for NDMA up to the end of shelf-life of the medicinal product should be demonstrated through appropriate data from batches of the medicinal product.
4. The MAH should implement a control strategy regarding N-nitrosamines for ranitidine containing medicinal products.

<u>For all other ranitidine containing products</u>

1. The MAH should submit quantitative data on the endogenous formation of NDMA in humans from ranitidine and demonstrate whether the results support a positive benefit-risk balance of the product.
2. A limit for NDMA should be set in the release specification of the medicinal product. This limit should take into account any increase in NDMA levels observed during stability studies. The limit at the end of shelf life should be based on the maximum daily dose of Ranitidine free base taking into account the route of administration in accordance with ICH M7(R1), with a maximum daily intake of NDMA of 96 ng/day.
3. Compliance with the limit for NDMA up to the end of shelf-life of the medicinal product should be demonstrated through appropriate data from batches of the medicinal product.

4. The MAH should implement a control strategy regarding N-nitrosamines for ranitidine containing medicinal products.