Assessment report

Referral under Article 31 of Directive 2001/83/EC

INN: ranitidine

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

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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[1] February 2021, formatting typo corrected on page 25

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1. Information on the procedure

N-Nitrosodimethylamine (NDMA), classified by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans" (Class 2A carcinogen)[2], was identified in September 2019 in Ranitidine Active Pharmaceutical Ingredient (API) batches and finished products available in the EU in levels that raised concerns according to the principles of ICH-M7. Scientific literature indicated 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).

In addition, *in vitro* studies with different pH solutions of ranitidine with and without nitrite have been carried out to evaluate if similar pH conditions as to the *in vivo* would lead to the formation of NDMA. Although the nitrite levels used were far above those usually present in the human stomach, the results seemed to indicate that NDMA could be formed from ranitidine at acidic pH in the presence of nitrite. Given these analytical results, it appeared that NDMA can also be formed from ranitidine during certain analytical procedures, especially those using high temperatures.

Based on the above, on 12 September 2019 the EC triggered a referral under Article 31 of Directive 2001/83/EC to assess the impact of these concerns on the benefit-risk balance of ranitidine-containing medicinal products and requested CHMP to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Ranitidine is an H2-receptor antagonist authorised since 1981 in the EU as a single agent in form of tablets, syrup or solutions for injection/infusion of different dosages.

Ranitidine-containing medicinal products are approved via National, Mutual Recognition and Decentralised procedures, in the following therapeutic indications:

75 mg Film-coated Tablets
Adults and children >16 years of age
- Treatment of acid indigestion and heartburn

150/300 mg Film-coated and effervescent Tablets, 150 mg/10 ml Syrup
Adults (18 years and over)
- Duodenal ulcer, benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents, recurrent ulcer, post-operative ulcer, reflux oesophagitis,
- Zollinger-Ellison syndrome, prophylaxis of recurrent haemorrhage from peptic ulcer, premedication in anaesthesia, prophylaxis of stress ulceration.
- Ranitidine is also indicated in those conditions such as gastritis and duodenitis when associated with acid hypersecretion.

Children (3 years to 18 years)
- Short-term treatment of peptic ulcer
- Gastro-oesophageal reflux treatment, including reflux oesophagitis and symptom relief in gastro-oesophageal reflux disease

10 mg/ml, 25 mg/ml Solution for Injection/Infusion

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[2] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 17 : Some N-Nitroso Compounds

Adults (18 years and over)
Acute attacks and exacerbations of:
- duodenal ulcer
- benign gastric ulcer
- recurrent ulcer
- post-operative ulcer
- reflux oesophagitis
- Zollinger-Ellison syndrome
- haemorrhage from peptic ulcer
- premedication in anaesthesia
- prophylaxis and treatment of stress ulceration

Children (6 months to 18 years)

- Short-term treatment of peptic ulcer
- Gastro-oesophageal reflux treatment, including reflux oesophagitis and symptom relief in gastro-oesophageal reflux disease

In July 2019, findings from a private laboratory in the United States (US) indicated that ranitidine can generate NDMA, classified by the IARC as "probably carcinogenic to humans" (Class 2A carcinogen), 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 the human stomach, the results seemed 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.

2.2. Criticality

For all indications alternative medicinal products are authorised in the EU albeit not in every individual country. Other H_2-receptor antagonists (e.g. famotidine, cimetidine) and proton pump inhibitors (PPIs) are available and may be used instead of ranitidine. It is however noted that not all H_2-receptor antagonists and PPIs are available or authorised for all indications in each Member State. Indications and patient populations treated may be different for available alternative H_2-receptor antagonists and PPIs within an individual Member State. Aforementioned differences underscore the importance of a criticality assessment of ranitidine at the level of an individual Member State. Ranitidine formulations were not considered critical by 19 out of responses from 29 EU/EEA countries and UK (65%). For 10

out of the 29 countries, one or more ranitidine formulations were considered critical in indications labelled for ranitidine. Respective Member States are Estonia, Germany, Ireland, Italy, Lithuania, Luxembourg, Malta, Portugal, Romania and Spain. Respective formulations used in label mainly concerned intravenous ranitidine formulations for paediatric use or for very ill patients in whom oral ranitidine administration is not possible.

2.3. Quality aspects

Introduction

One aspect that has been considered within this referral procedure is the type and extent of contamination with potential carcinogenic nitrosamines, especially with NDMA in ranitidine-containing drug products.

CEP applications for ranitidine

All seven Certificates of Suitability to the monographs of the European Pharmacopoeia (CEPs), from 6 CEP holders, that were valid at the beginning of the referral have been assessed and have been suspended by the EDQM or withdrawn by the holder, due to the presence of NDMA in the drug substance. As a result, there is at the time of this assessment report no valid CEP for ranitidine available.

In general, the following conclusions can be drawn from the information provided by EDQM:

- It is possible to manufacture ranitidine hydrochloride (HCl) batches, with NDMA levels below a limit of 0.16 ppm (based on ranitidine HCl),

- However, an increase in NDMA levels is observed over time. Storage conditions (temperature, humidity) impact the rate of formation of NDMA.

- No clear root cause has been identified, so far, and it is not clear for how long batches may stay within the acceptable limit for NDMA. Further studies are needed to further characterise the degradation profile of ranitidine.

Testing results

API

Several companies, as well as the Food and Drug Administration (FDA), have reported the formation of high levels of NDMA when ranitidine is exposed to high temperatures (>100°C), as it occurs when it is used during analysis for NDMA based on gas chromatography (GC). Therefore, the GC-MS method, originally developed for the analysis of nitrosamines in the sartans, appears not to be suitable for the analysis of ranitidine. Analysis of NDMA content in ranitidine should therefore be performed with analytical methods that separate ranitidine and NDMA at low temperature (<~40°C).

Drug substance manufacturers have not yet defined the root causes for the presence of NDMA in their drug substances; however, the following possible root causes have been identified and are under further investigation:
- the potential degradation of the API,
- the presence of NDMA within regulatory intermediates,
- the presence of nitrogen oxides within the regulatory starting materials, or their precursors,
- the presence of chloramine in purified water.

In addition, results from other international regulators are in line with results reported by several MAHs that at high temperature and high humidity, the degradation of ranitidine with the formation of NDMA is substantial.

<u>Finished Products</u>

Many MAHs have, so far, not tested their drug products for the presence of NDMA and fully relied on testing of the drug substance. From the results of the drug substance, it is known that NDMA concentration may increase over time, possibly due to instability of the drug substance. For drug products, this upward trend in the amount of NDMA present is not as clear as for the drug substance; however, more information on the formation of NDMA in the drug products is required.

Therefore, all MAHs were requested during the referral procedure to test their drug products for the presence of NDMA. The sampling strategy include drug products of different age, i.e. freshly prepared drug product batches, drug product batches towards the middle of their approved shelf-life, as well as batches near the end of their approved shelf-life, in order to demonstrate that NDMA content will not increase during storage of the drug product, or that the level will stay within acceptable limits during the shelf-life of the drug product.

Almost for all drug products tested so far, NDMA has been identified in levels above the current limit of 0.16 ppm established according to the principles of ICH-M7 considering an acceptable intake of 96 ng/day NDMA, a maximum daily dose of 600 mg and lifelong treatment.

During the Oral Explanations, the MAHs shared with the Committee preliminary stability testing results indicating that the level of degradation in aqueous phase (for the IV formulation) appears less pronounced than in solid phase (oral formulation).

Potential mechanism

Several MAHs have postulated that based on the obtained results for drug products and drug substances it is likely that NDMA is formed by degradation of ranitidine (see structure below), without the presence of additional source(s) of nitrite.
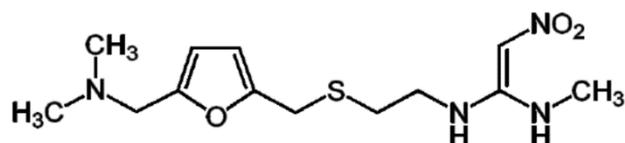
One MAH provided results of studies with isotopically-labelled drug substance performed to determine the root cause of the presence of low levels of N-nitrosodimethylamine (NDMA) in ranitidine drug substance and products. One study was carried out with labelled material under stressed testing conditions while a further study aimed to determine whether the formation of NDMA was an intramolecular process where reaction occurred within a single molecule, or an intermolecular process where the dimethylamino- and nitro groups were derived from separate molecules. The obtained results provided strong evidence that the formation is an intermolecular reaction and not an intramolecular reaction and that no external nitrosating agent is needed. However, it has not been possible to define an exact mechanism for the degradation reaction. There is evidence that two independent degradation reactions occur and the by-products from those reactions could then combine to form NDMA, although other possibilities may exist.

Furthermore, it was proposed that solid state properties do impact the formation of NDMA from the drug substance, and thus may impact the stability of the drug substance. The solid-state properties were impacted by the method of crystallisation.

As the drug substance remains in the solid-state in the tablet product, an increase in NDMA could be expected. For the solution and syrup products where the drug substance is dissolved, it is possible that the degradation pathway described above may not occur.

A review of testing data further indicated that in most examples where the drug product and drug substance NDMA content has been measured within the same period, the amount in the drug product is in general lower than in the corresponding API. This indicates the rate of increase in drug product is slower than in API, but this has still not been confirmed experimentally for any specific formulation.

Finally, it was concluded from experiments that the reaction of ranitidine with sodium nitrite/nitrous acid is instantaneous and not consistent with the slow formation of NDMA over a prolonged period, as observed in all batches during stability studies.

It was also concluded that NDMA is formed in ranitidine drug substance primarily due to an internal degradation mechanism that occurs in the solid state. The degradation proceeds without participation of any extraneous impurities. Elevated temperature and relative humidity both contribute to an increase in the rate of degradation.

Discussion on quality

Based on the available results received, it appears that NDMA is formed over time from ranitidine itself. From the data submitted during the procedure and from OMCL testing, it appears that the solutions for injection/infusion have lower levels of NDMA contamination than the oral forms, especially the tablet forms, however the rate of increase in NDMA in liquid formulations over time and until end of shelf life is not established. For oral solutions, very little data is available to draw any conclusions.

It should be noted that degradation of ranitidine and formation of NDMA in drug products appears to be slower than in the isolated drug substance. However, this conclusion is based on limited data and available drug product testing results are not sufficient to conclude if degradation of ranitidine in the drug product to form NDMA is a general phenomenon or is depending on the source of drug substance and composition of the drug product, or to define root causes.

The formation of NDMA due to an intermolecular reaction has been proposed as a potential mechanism, however two independent degradation reactions may occur and products from these reactions could then combine to form NDMA, although other possibilities may exist.

So far, insufficient data is available on the kinetics of NDMA formation over time in drug products to draw any general conclusions on the extent of formation of NDMA over time in ranitidine and if the amount of NDMA in drug products can be sufficiently controlled over shelf-life. Further data are needed to characterise this risk and ensure that drug products comply with acceptable release and shelf-life limits.

2.4. Non-clinical aspects

Genotoxicity

GSK submitted available data on genotoxicity that were performed with ranitidine and its main metabolites. These data did not indicate relevant genotoxic potential. A weak positive signal in the absence of metabolism only occurred at a concentration thousands of times higher than the therapeutic concentrations. This signal was observed at a concentration in excess of the required maximum concentration of 5 mg/plate in the Ames assay. Consequently, this weak positive signal is not considered of clinical relevance.

Potential formation of a mutagenic nitrosation product, N-nitroso-nitrolic acid derivative (AH23729) only occurred to a significant level at low pH and at nitrite concentrations which are far in excess of those that can be expected under physiological conditions. It is therefore unlikely that AH23729 would contribute to any potential for genotoxicity of ranitidine in patients.

Ranitidine also did not indicate genotoxicity in a series of *in vivo* studies, including a male rat dominant lethal assay (single oral dose of ranitidine 1000 mg/kg); a mouse bone marrow micronucleus test (two i.p. doses of 3, 10 and 30 mg/kg ranitidine HCl); a rat stomach unscheduled DNA synthesis assay (single oral doses of ranitidine HCl of 30, 100, 200 mg/kg); and a cytogenetic study in spermatogonia cells of mice (oral dosing).

Carcinogenic potential in rodent studies with ranitidine

The carcinogenic potential of ranitidine was investigated in life-time studies in mice and rats treated with ranitidine (dosed up to 2000 mg/kg/day) and there was no indication of tumorigenic or carcinogenic effects in any of the studies conducted. The generation of NDMA and DMA was not specifically investigated in these studies, but nitrosation reactions have been considered. If mutagenic nitrosation products would have been formed in significant amounts, it may be expected that this would be reflected by a carcinogenic signal in the carcinogenicity assays. The apparent absence of a signal shows that these nitrosation products were not formed, or if nitrosation products have been formed, this only occurred at a level not leading to a significant increase in tumours. The detection limit in terms of increases of tumour incidence in the carcinogenicity assays is usually in the range of 2% (for rare incidental tumour types) to 10% or more (for tumour types with a significant background level). Therefore, these studies do not inform on increased risks below these percentages that may occur at low exposure rates.

Gastric carcinoids were observed in two additional rat studies at high doses (WPT/94/381 and WPT/93/096) following the dietary administration of high doses of either ranitidine hydrochloride or ranitidine bismuth citrate which resulted in extensive and prolonged systemic exposure resulting in continuous acid inhibition and hypergastrinemia.

The latter results reported by GSK are supported by those reported in a study by Havu et al. In 100 rats, it was shown that 106 weeks of treatment with ranitidine (2g/kg/day) resulted in acid inhibition which was associated with an approximately 3-fold increase in plasma gastrin which persisted throughout the whole period of the study. The ranitidine treatment resulted in a pronounced hyperplasia of gastric ECL cells. Carcinoids were found in 19 rats, 4 of which were micro-invasive. No carcinoids were found in the control animals. The results provide support for the gastrin mechanism, i.e. that the development of ECL-cell carcinoids in the rat gastric mucosa is a consequence of prolonged hypergastrinaemia and is not a unique effect of any individual acid-inhibiting drug.

Some experimental data in non-clinical models have been published (Rogers et al 2018 [3]; Vila-Leahy et al., 2016 [4]) suggesting H_2-receptor antagonists (H2RAs) could have a protective role in breast cancer. However, the clinical relevance of these data is not known.

Formation of NDMA or other potentially mutagenic nitroso compounds

The formation of NDMA as an impurity in drug substance or drug product is discussed in the quality section.

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[3] Rogers D, Vila-Leahey A, Pessôa AC, Oldford S, Marignani PA, Marshall JS. Ranitidine Inhibition of Breast Tumor Growth Is B Cell Dependent and Associated With an Enhanced Antitumor Antibody Response. Front Immunol. 2018 Aug 15;9:1894. doi: 10.3389/fimmu.2018.01894. eCollection 2018.
[4] 12. Vila-Leahey A, Rogers D, Marshall JS. The impact of ranitidine on monocyte responses in the context of solid tumors. Oncotarget. 2016 Mar 8;7(10):10891-904. doi: 10.18632/oncotarget.7211.

In this section, the potential formation of NDMA or other potentially mutagenic nitroso compounds after administration to patients is discussed.

The formation of NDMA or other potentially mutagenic nitroso compounds could theoretically occur in several ways:

1. Chemical conversion of ranitidine in the stomach or intestine

2. Generation of NDMA and metabolism of ranitidine by the gastrointestinal microflora

3. Metabolism of ranitidine in the liver or other tissues

4. Further chemical or metabolic conversion of ranitidine or its metabolites in the bladder

Below these theoretical possibilities are discussed:

1. <u>Chemical conversion of ranitidine in the stomach or intestine</u>

In simulated gastric conditions with nitrite levels of 200 mM, nitroso-compounds are formed (Martelli et al 1983)[5]. Similar findings were reported by others with excess nitrite concentration (Maura et al, 1983[6]; De Flora et al, 1983[7]). These nitroso-compounds showed genotoxic activity in rat hepatocyte DNA repair assay over a range of 0.02 – 0.2 mM. GSK (Brittain et al 1981)[8], claimed an (instable) nitroso-nitrolic acid derivative of ranitidine with mutagenic activity was only produced after incubation in the presence of 40 mM nitrite and not in the range of 2-20 mM.

O'Connor et al (1987)[9] did not find any evidence of increased mutagenicity in gastric aspirate from 18 patients after treatment with cimetidine of ranitidine. These results conflict with those reported by Özhan and Alpertunga (2003)[10] who found genotoxic activity of nitrite-ranitidine reaction products generated under simulated gastric conditions at a nitrite concentration of 8.8 mg/L (0.13 mM) when assayed in the *umu*-assay. In the study from Özhan and Alpertunga (2003) no analytical results were reported identifying the genotoxic substances and thus the claim that genotoxic nitroso derivatives were formed was not further substantiated by these authors.

The paper from Zeng and Mitch (2016)[11] reports the formation of NDMA *in vitro* where gastric conditions were simulated. At 5 mM nitrite concentration and pH 2 the NDMA concentration found was 57 µM, which declined to <0.01 µM at pH 5.25. The incubation period was 24 hours. The proposed *in vitro* conversion of NDMA from ranitidine is nitrosation of diethylamino-containing moiety in ranitidine, forming an unstable tertiary N-nitrosamine. This unstable intermediate can undergo dealkylation to release dimethyl amine (DMA), which in turn nitrosated to form NDMA, a stable secondary N-nitrosamine (see figure below).

In-vitro conversion of NDMA from ranitidine:

[5] Martelli, A., Fugassa, E., Voci, A. and Brambilla, G. (1983) Unscheduled DNA synthesis induced by nitrosated ranitidine in primary cultures of rat hepatocytes. Mutat. Res., 122, 373–376.
[6] Maura, A. et al. (1983) DNA damage induced by nitrosated ranitidine in cultured mammalian cells. Toxicol. Lett., 18, 97–102.
[7] De Flora, S., Bennicelli, C., Camoirano, A. and Zanacchi, P. (1983) Genotoxicity of nitrosated ranitidine. Carcinogenesis, 4, 255–260.
[8] Brittain, R.T. et al. (1981) Safety of ranitidine. The Lancet, 318, 1119.
[9] O'Connor, HJ, Riley, SE, Axon, AT and Garner, RC (1987). "Effect of histamine H2-receptor antagonist therapy on the mutagenic activity of gastric juice." Mutat Res 188(3): 201-208.
[10] Özhan G, Alpertunga B (2003) Genotoxic activities of drug-nitrite interaction products Drug Chem Toxicol 26, 295-308
[11] Zeng T, Mitch W. Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. Carcinogenesis. 2016;37(6):625-634.
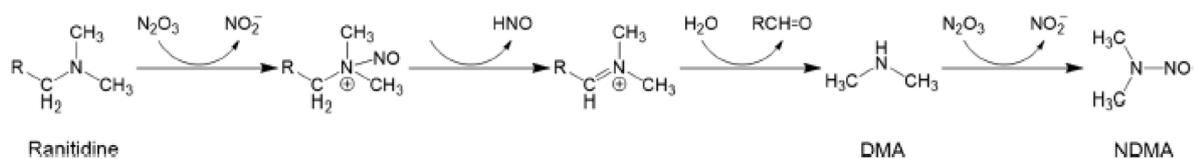
Taken together, it appears that under simulated intragastric conditions NDMA formation (or other nitroso compounds) from ranitidine only occurs at nitrite concentrations far in excess of those that may exist under normal physiological concentrations.

2. <u>Generation of NDMA and metabolism of ranitidine by the gastrointestinal microflora</u>

The effect of four weeks administration of ranitidine (150 mg twice daily) on gastric bacterial flora in healthy volunteers was studied. Total gastric bacterial counts were increased at the end of the treatment; one-third of all the bacterial strains isolated from gastric juice were species able to convert ingested nitrates to nitrites. However, almost all members of predominant species from gastric juice i.e. *Corynebacterium spp* and *Streptococcus spp* did not reduce nitrate.

The presence of nitrate-reducing bacteria may increase nitrite concentrations and subsequently, a rise in nitrosamines in general. Results of a study by Matsuda et al. (1990)[12] indicated that patients with gastric ulcer had higher detection ratios and concentrations of NDMA and NDEA in gastric juice and small, but significant increases occurred during treatment with histamine H2-receptor antagonists (cimetidine, roxatidine, famotidine and ranitidine). As mentioned, patients with gastric ulcers had higher concentrations of NDMA and NDEA in gastric juice and while significant increases occurred during treatment with ranitidine, the extent of that increase was below levels which are regarded as toxic or have been experimentally proven to be carcinogenic. Nevertheless, the authors caution against long-term exposure to low levels of nitrosamines. The gastric juice maximum concentrations of NDMA and NDEA were 7.9 and 9.8 ng/ml in patients, and 1.2 and 1.3 ng/ml in healthy subjects. Furthermore, there was no particular difference among any of these H2RAs, which would suggest that the nitrosamines are generated through other mechanism and not dependent on the chemical structure of the H2-receptor antagonist.

These results were in line with Krawczyński et al. (2002) [13] evaluating the concentration of nitrosamines in the gastric juice in children with chronic gastritis (CG) before and after treatment. However, this study did provide a combined concentration measurement without the results of individually measured nitrosamines concentrations. The concentration of nitrosamines was examined before and 4-6 weeks after eradication treatment (ranitidine, amoxicillin, nitroimidazole). After treatment statistically significant increase of nitrosamine concentration in the gastric juice (1.031 mg/l) was found, particularly in boys (1.499 mg/l) in comparison with the values obtained before treatment (0.074 mg/l) and with to the control group (0.063 mg/l), and an age-matched group of girls (0.924 mg/l). It was found that nitrosamine concentrations in gastric juice in children with CG were similar to the values obtained in the control group. After treatment, a significant increase of nitrosamine concentration in gastric juice was found. The lack of reporting on individual nitrosamines and the long period between treatment and post-treatment assessment of nitrosamines makes it difficult to draw conclusions from this study.

Thomas et al. studied effects of one year's treatment with ranitidine and of truncal vagotomy on gastric contents. The biochemical and microbiological changes recorded during one-year of treatment

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[12] Matsuda, J. et al. (1990) N-Nitrosamines in gastric juice of patients with gastric ulcer before and during treatment with histamine H2-receptor antagonists. Gastroenterol. Jpn., 25, 162–168.
[13] Krawczyński M, Ignyś I, Borucki M (2002) [Abstract] Nitrosamines in children with chronic gastritis Pediatria Polska 77, 217-224

with ranitidine were similar to the findings in patients after truncal vagotomy. Treatment with ranitidine or vagotomy was associated with significant increases in pH, nitrite concentration and bacterial counts. However, there was no significant correlation between pH and N-nitroso-compound concentration or between concentrations of nitrite and N-nitroso compounds [Thomas et al., 1987][14]. The study by Thomas et al. is also cited in a publication by Penston et al., which indicates several studies that have shown that both short term and long-term use of H2RAs rarely reduce gastric acidity sufficiently to permit bacterial overgrowth and ranitidine used in the therapeutic doses does not result in excessive bacterial colonization of the stomach [Penston J, Wormsley KG.,1986].[15]

Garcia Del Risco (1984)[16] determined the influence of 24 h of ranitidine treatment (150 mg b.i.d.) on gastric bacterial flora and N-nitroso compound formation. During ranitidine treatment, the nitrite/nitrate ratio was positively correlated with intragastric pH and with the nitrate-reducing organism count of the placebo period. However, the mean intragastric concentrations of nitrate, nitrite, N-nitroso compounds and counts of nitrate-reducing organisms were not significantly altered by ranitidine, but there was a statistically significant rise in the number of total bacteria. These results may indicate that the reduction of nitrate to nitrite required the combination of two factors: a high count of nitrate-reducing organisms before treatment and a high intragastric pH.

Of note, Sharma et al. reported that fasting pH, bacterial counts, percentage of nitrate-reducing bacteria, nitrite concentrations and N-nitroso compound concentrations were significantly increased 22 hours after a dose of omeprazole [Sharma et al., 1984][17]. Bacterial nitrosation is more likely to occur at a neutral pH [Sanduleanu S et al., 2001][18]. According to the study results by Kato N et al. the gastric pH of patients who were receiving an H2RA (21 cases) ranged from 1.91 to 6.51 (mean, 4.32), with gastric pH > 5.00 seen in 10 cases [Kato N, et al., 1986] [19]. Importantly, infection with Helicobacter pylori is likely to increase NO production from macrophages in response to bacterial overgrowth, so that the availability of NO in Helicobacter pylori-infected individuals will be increased, which may further influence the formation of nitrosamines and influence its background level [Jakszyn P, et al., 2006] [20]. However, Houben et al (1996)[21] reported that an increase of the intragastric pH up to pH 6.0 and the subsequent bacterial growth does not automatically lead to high concentrations of nitrosamines.

There is scant information on the metabolism of ranitidine by the gut microflora. Ranitidine is metabolised by the gut microflora[22], possibly via cleavage of an N–oxide bond from the diaminonitroalkene region of ranitidine molecule. However, due to the lack of available data it is unknown whether DMA or NDMA can be formed as a result of metabolism of ranitidine by gastrointestinal microflora.

3. Metabolism of ranitidine in the liver or other tissues

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[14] Thomas, J.M. et al. (1987) Effects of one year's treatment with ranitidine and of truncal vagotomy on gastric contents. Gut, 28, 726–738.
[15] Penston J, Wormsley KG. H2-receptor antagonists and gastric cancer. Med Toxicol Adverse Drug Exp 1986;1(3):163-168.
[16] Garcia del Risco, F. et al. (1984) Influence of ranitidine during a 24-hour period on the level of nitrites, nitrates, nitrosamines and bacterial flora in the gastric juice of healthy subjects. Gastroenterol. Clin. Biol., 8, 749– 753.
[17] Sharma, B.K. et al. (1984) Intragastric bacterial activity and nitrosation before, during, and after treatment with omeprazole. Br. Med. J., 289, 717– 719.
[18] Sanduleanu S, Jonkers D, de Bruïne A, Hameeteman W, Stockbrügger ,R.W. Changes in gastric mucosa and luminal environment during acid-suppressive therapy: a review in depth. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2001,11;33(8):707-19.
[19] Kato N, Watamabe K, Ueno K, Ito Y, Muto Y, Kato H, et al. Gastric microflora in patients receiving H2-blocker. Kansenshogaku zasshi.The Journal of the Japanese Association for Infectious Diseases 1989 07;63(7):726-31.
[20] Jakszyn P, Bingham S, Pera G, Agudo A, Luben R, Welch A, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. Carcinogenesis 2006 07;27(7):1497-1501.
[21] Houben GM, Hooi J, Brummer RJ, Stobberingh EE, Stockbrügger RW (1996) Are intragastric N-nitroso compounds elevated after short-term acid suppression? Eur J Cancer Prev 5 Suppl 1:83-7
[22] Basit AW and Lacey LF. Colonic metabolism of rantidine: Implications for its delivery and absorption. International Journal of Pharmaceutics, 2001;227:157-65

There are good correlations in ranitidine disposition and ADME characteristics between human and preclinical species, as well as between *in vitro* and *in vivo*; oral ranitidine has a moderate absorption. Hepatic metabolism plays a minor role in the overall clearance, catalysed by microsomal enzymes FMO3 and FMO5 and CYP2C9, 1A2 and 2D6. The principal route of excretion is the urine. In human, approximately 30% of the oral dose is accounted for as unchanged drug in the urine, followed by minor components of metabolites N-oxide (about 4-6%), S-oxide (about 1-2%) and desmethyl-ranitidine (about 1-2%) and furoic acid analogue (1-2%) of ranitidine (see metabolism pathways in figure 1). The furoic acid analogue is formed by oxidative deamination. It would be predicted that formation of this metabolite, as postulated via oxidative deamination, may also result in the release of dimethylamine (DMA), which may be available to form NDMA on exposure to nitrite. However, in publications reporting metabolism data in humans [Bell, 1980[23]; Carey, 1981 [24]; Martin, 1981[25]; Martin, 1982[26]] the furoic acid analogue of ranitidine was not detected, possibly due to its low abundance.

Figure: Metabolism of ranitidine.
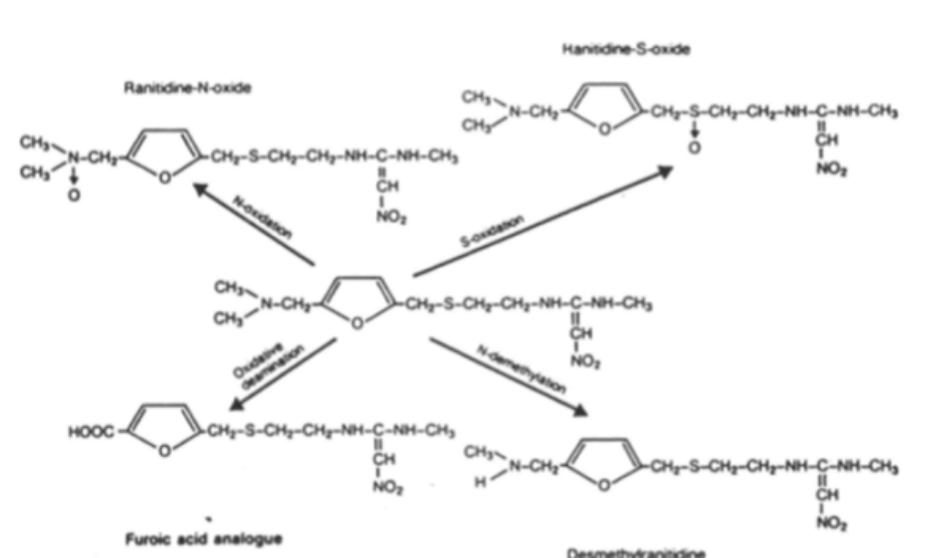
It has been hypothesised that ranitidine could be substrate for N(G), N(G)-dimethylarginine dimethylaminohydrolase (DDAH), leading to the generation of DMA, which could subsequently react to form NDMA in the presence of a nitrosating source. However, this hypothesis about DMA formation from ranitidine via metabolism by DDAH-1 is unsubstantiated by empirical data.

It has been argued that differences exist between ranitidine metabolism after oral and parenteral administration. Indeed, after IV administration of 150 mg ranitidine, 79% of the dose was recovered in urine. After oral administration of 150 mg ranitidine, 27% of the dose was recovered in urine (van Hecken 1982 [27]). After i.v. administration a larger fraction or ranitidine is excreted as parent compound (Carey et al 1981 [22]). These differences reflect first-pass metabolism and/or metabolism by the intestinal flora. NDMA has not been measured in these old pharmacokinetic studies and may have

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[23] Bell JA, Dallas FA, Jenner WN, Martin LE. The metabolism of ranitidine in animals and man [proceedings]. Biochem Soc Trans 1980; 8(1):93.

[24] Carey PF, Martin LE and Owen PE. Determination of ranitidine and its metabolites in human urine by reversed-phase ion-pair high-performance liquid chromatography. Journal of Chromatography B: Biomedical Sciences and Applications, 1981;225:161-8

[25] Martin LE, Oxford J and Tanner RJN. The use of on-line high-performance liquid chromatography-mass spectrometry for the identification of ranitidine and its metabolites in urine. Xenobiotica, 1981;11:831-40

[26] Martin LE, Oxford J and Tanner RJN. Use of high-performance liquid chromatographymass spectrometry for the study of the metabolism of ranitidine in man. Journal of Chromatography, 1982;251:215

[27] Br J Clin Pharmacol. 1982 Aug;14(2):195-200. Ranitidine: single dose pharmacokinetics and absolute bioavailability in man.

been missed if it is formed as a minor metabolite. Although the quantity of ranitidine metabolised is lower after parenteral administration, it is still uncertain whether less NDMA will be formed from ranitidine after parenteral administration (if endogenous formation indeed occurs). Due to the lack of available data it is currently not clear if the route of administration has an impact on the endogenous formation of NDMA from ranitidine.

4. <u>Further chemical or metabolic conversion of ranitidine or its metabolites in the bladder</u>

The metabolites in urine have been analysed and encompass besides the parent compound ranitidine, ranitidine N-oxide, ranitidine S-oxide and desmethyl ranitidine (Carey et al, 1981). GSK also reported a furanoic acid derivative of ranitidine as a minor metabolite. The latter metabolite would also indicate that DMA is generated, which once excreted into the urine could be nitrosylated in the presence of sufficient quantities of nitrite (see also under point 3). However, whether this reaction takes place and may lead to significant quantities of NDMA in the urine is uncertain. Zeng and Mitch (2016) suggested the presence of NDMA in human urine after ingestion of ranitidine resulting in a 430-fold increase of urinary NDMA. Also Krawczyński et al (2002) evaluating the concentration of nitrosamines in the urine in children with chronic gastritis (CG) before and 4-6 weeks after eradication treatment (ranitidine, amoxicillin, nitroimidazole) observed an increase in nitrosamines (about 10 –fold), however this study did provide a combined concentration measurement without the results of individually measured nitrosamines.

However, the absence of a clear signal indicating an increased risk for bladder cancer in patients taking ranitidine (see discussion on epidemiological data in the clinical section) does not support the results of Zeng and Mitch (2016) which claim to have found a 430-fold increase of urinary NDMA. Similarly, rat carcinogenicity studies have not shown an increase in renal or bladder tumours. Whether marginally increased levels of NDMA may occur has not been investigated by any MAH. The discordant outcome of the study by Zeng and Mitch (2016) might be caused by analytical confounding due to the methodologies used.

<u>Conclusion on endogenous formation of NDMA from ranitidine:</u>

From literature data, it is clear that overall the effects of ranitidine treatment on nitrosamine formation *in-vivo* or *in-vitro* have been investigated repeatedly, primarily focussing on the nitrosamine formation in the stomach. However, many studies have limitations and no definite conclusions can be drawn from these data since results are diverse with some studies reporting increased nitrosamine formation in the stomach (Matsuda et al. (1990) and Krawczyński et al. (2002)) while others did not find this effect [Garcia Del Risco (1984), Thomas et al. (1987), Houben et al. (1996)], and some do report increased excretion in the urine [Krawczyńki et al. (2002, Zeng and Mitch (2006)]. Different results might be explained by the fact that the nitrosamine formation seems to be a multifactorial process with different factors involved such as stomach pH and nitrate and nitrite levels in the stomach. Furthermore, nitrosamine formation in the stomach is reported not only for ranitidine but also for other H2-receptor antagonists, suggesting other mechanisms may be responsible [Matsuda et al (1990)].

There is scant information on the metabolism of ranitidine by the gut flora. DMA may possibly be formed by *in vivo* metabolism through oxidative deamination. Whether this would result in increased NDMA levels in the urine would depend on the conditions in the bladder.

In addition, due to the lack of available data it is currently not clear if the route of administration has an impact on the endogenous formation of NDMA from ranitidine.

The final risk assessment could benefit from further *in vivo* investigations in humans employing labelled ranitidine, where the fate of the relevant nitrogen atoms can be traced. Using the stable isotope ^{15}N would make it possible to administer sufficient amounts to also detect low quantities of

NDMA. Measurement of both [^{15}N]-NDMA and [^{14}N]-NDMA would make it possible to differentiate between NDMA derived from ranitidine and NDMA coming from other sources.

Risk assessment of NDMA

Acceptable intake

NDMA is a potent mutagenic carcinogen in a number of different animal species. On the basis of animal data (rat being the most sensitive species), NDMA is classified by the IARC as "probably carcinogenic to humans" (Class 2A carcinogen). This classification is used by IARC when there is "limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals". Other long-term effects, such as severe hepatotoxicity have also been observed in rhesus monkeys with this class of nitrosamines.

Although NDMA itself does no react with DNA and metabolic activation is needed to form the DNA-reactive molecule, in risk assessment NDMA is regarded as a DNA reactive carcinogen. The paradigm generally used for risk assessment of such compounds is based on the assumption that there is no biological threshold for DNA reactive carcinogens and any exposure level is considered to pose a risk and a level without a risk cannot be established. This general paradigm has been challenged on scientific grounds. However, to depart from this paradigm and establish a level below which no risk is anticipated, mechanistic and compound-specific data would be needed to provide convincing evidence for such a threshold. Furthermore, it needs to be considered that for NDMA and nitrosamines, in general, there is a considerable level of background exposure. Background exposure may occur both from other exogenous sources and from endogenous formation. The estimates on the levels of background exposure are affected by many factors (e.g. food and lifestyle factors), and there is large variability in estimates on the level of endogenous NDMA formation. Nevertheless, additional exposure may be expected to add to the risk and should be accounted for.

An increased theoretical lifetime cancer risk of 1 additional case in 100,000 treated patients, i.e. increased lifetime cancer risk of 1:100,000, is the generally accepted risk level for mutagenic impurities in pharmaceutical products (ICH M7(R1) guideline).

NDMA belongs to N-nitroso compounds, which are part of the so-called "cohort of concern" described in the ICH guideline M7(R1). For such compounds the generic Threshold of Toxicological Concern (TTC) of 1.5 µg/day as an Acceptable Intake (AI) for mutagenic impurities is not considered applicable and a compound specific AI needs to be derived from compound specific carcinogenicity data.

The generally accepted approach recommended by ICH M7(R1) is to use either the dose giving a 50% tumour incidence (TD50) or the Bench Mark Dose Lower Bound Confidence Limit (BMDL10), an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents, as the point of departure for the calculation of excess cancer risk.

A well-acknowledged and accepted source for TD50 values from cancer studies is the Carcinogenic Potency Database (CPDB; online)[28].

The TD50 listed in said database for NDMA is 0.096 mg/kg/day (in the most sensitive species, the rat) calculated as harmonic mean from all positive studies in rats including the data of the Peto et al. 1991[29] study. The extrapolation to the excess risk level for cancer is performed by linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD50 by 50,000 (50% or 0.5 x 100,000). For NDMA this translates into a dose of 1.92 ng/kg/day. For a person with a

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[28] Fitzpatrick RB: CPDB: Carcinogenic Potency Database. Med Ref Serv Q. 2008 Fall;27(3):303-11

[29] Peto R., Gray R., Brantom, P. and Grasso, P. (1991). Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. Cancer Res. 51, 6452–6469

bodyweight of 50 kg this would result in an AI level of 96 ng/day (50 x 1.92 ng). 96 ng/day correspond to 0.16 ppm for ranitidine base when a life-time exposure is considered, with a daily dose of 600 mg ranitidine.

Less than lifetime (LTL) approach

Several MAHs argued that the LTL approach can be applied to the case of ranitidine since the AI derived for ranitidine (96 ng/day) is calculated for lifetime exposure and MAHs claimed that most patients will use ranitidine for only a limited period of time. The LTL approach is explained in the ICH M7(R1) guideline. The arguments from MAHs have been considered by the CHMP but the Committee concluded that they do not justify setting higher limits in view of the risks of NDMA and benefits of ranitidine, but also that the use might be repeated or be chronic. Consequently, the CHMP considered that a limit for NDMA in ranitidine shall be based on the maximum daily dose, assuming exposure throughout life. A limited duration of use of ranitidine would further mitigate the actual risks for the patients, but it does not justify the setting higher limits for NDMA in ranitidine.

The relevance of endogenous formation of NDMA from ranitidine to the risk assessment

As discussed in previous sections there is uncertainty on whether NDMA can be formed *in vivo* from ranitidine, however, a possible endogenous formation of NDMA arising from ranitidine cannot be excluded. Additional data clarifying if, to which extent and where *in vivo* formation of NDMA from ranitidine actually occurs are needed.

Discussion on non-clinical/toxicology aspects:

Background exposure to NDMA occurs through food, water and the environment, or by endogenous formation. The estimates on the levels of background exposure are affected by many factors (e.g. food and lifestyle factors)[30] [31] and there is large variability in estimates on the level of endogenous NDMA formation[32]. Therefore, the extent of the external and endogenous NDMA exposure under normal circumstances as well as after administration of ranitidine is not clearly established.

The impact of NDMA on human health is currently only extrapolated from animal studies. However, as the DNA damage mechanisms documented in these studies are also relevant in humans and *in vitro* data in human cells are not significantly different from those in animal cells, it is prudent to assume that effects seen in animals may also occur in humans after exposure to sufficiently large amounts of nitrosamine. 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. Further, the target organ(s) of NDMA toxicity in humans are still not sufficiently clear.

A full risk assessment for patients previously exposed to NDMA impurities in ranitidine is not possible as the real extent of exposure of patients including endogenous NDMA formation is unknown. A risk assessment can only be based on a potential worst-case scenario.

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[30] Gushgari A., Halden R.: Critical review of major sources of human exposure to N-nitrosamines. Chemosphere. 2018 Nov;210:1124-1136. doi: 10.1016/j.chemosphere.2018.07.098. Epub 2018 Jul 20.

[31] Fristachi A1, Rice G. Estimation of the total daily oral intake of NDMA attributable to drinking water. J Water Health. 2007 Sep;5(3):341-55.

[32] Zeilmaker et al. Risk Assessment of N-nitrosodimethylamine Formed Endogenously after Fish-with Vegetable Meals. Tox. Sciences 2010, 116:323-35

2.5. Clinical aspects

2.5.1. Efficacy

Within the EU ranitidine is indicated in adults and children in the indications stated in section 2.1 above. No new data for efficacy has been submitted and assessed within this procedure.

It is noted that the authorized ranitidine formulations, the indications, and other aspects of the ranitidine SmPC vary across European Member States. Usual ranitidine dosages range from 150 mg to 6 g daily. Treatment duration is between 8-12 weeks however with recurring duodenal ulcer treatment duration can be up to 12 months. For hypersecretory conditions, the maintenance duration might be lifelong.

In the World Health Organization's Model List of Essential Medicines ranitidine is listed as essential medicine, regardless of the dosage form.

2.5.2. Safety

Post marketing safety data

Several MAHs have submitted cumulative overviews of clinical studies, post-marketing cases reporting *Neoplasms benign, malignant and unspecified (incl. cysts and polyps),* as well as epidemiological studies evaluating the risk of cancer following ranitidine use.

The reviews of post marketing cases provided only limited information, as the majority of case reports did not include detailed information about medical history and underlying diseases, time to onset, concomitant medications, potential confounding risk factors (such as smoking or obesity) or duration of use and indication of ranitidine therapy.

Additionally, there is a number of cases where the patients had well-known risk factors for specific cancer, therefore they are confounded by disease/pre-existent condition.

Taking into consideration the most consensual hypotheses for mechanisms of action of potential NDMA formation (e.g. by nitrosation under stomach-relevant pH conditions in vitro), the focus of EMA's analysis in the EudraVigilance (EV) database was on specific types of neoplasm such as renal and bladder neoplasms.

In this sense, and although it is difficult to highlight specific types of neoplasms without a causal association assessment of the cases, in EV data an emerging pattern in terms of disproportionality associated with specific types of neoplasms grouped under the "benign neoplasm gastrointestinal and renal" High Level Group Terms (HLGTs) could be seen which may well be due to a potential protopathic bias or reverse causality. In this case one of the limitations can be a protopathic bias due to the potential use of H2-receptor antagonists in response to symptoms caused by undiagnosed tumours which may lead to the erroneous conclusion that the medicinal product caused the tumour.

This is particularly a problem in studies of drug-cancer associations and other outcomes with long latencies. Nevertheless, it needs to be highlighted that the number of neoplasm cases is low, specially taking into account the high patient exposure data for some of the active substances in the class (i.e. famotidine and ranitidine).

Based on the cumulative reviews of post-marketing reports and epidemiological data currently available on H2- receptor antagonists and cancers overall, there were relatively few studies identified for each cancer type and no clear pattern emerged across cancer types or studies focused on specific cancer types.

As highlighted above, most of the information on the post marketing cases is limited since the majority of reports does not include detailed information about medical history and underlying diseases, time to onset, concomitant medications, potential confounding risk factors (such as smoking or obesity) or duration of use and indication of ranitidine therapy. Therefore, making a causality assessment is challenging.

Overall, no evidence relevant for the analysis has been identified from post-marketing cases, but the inherent limitations of spontaneous reporting in detecting carcinogenicity should be considered, mainly due to the long latency of the event. No conclusion can therefore be drawn based on the review of the spontaneously reported post-marketing cases.

There are very few relevant epidemiological studies to analyse and when performed, the data is limited and its interpretation is challenging as the majority of studies is not able to confirm or exclude the association between the ranitidine use and the risk of cancer. Some MAHs referenced overviews of available studies, e.g. from a systematic review and meta-analysis of observational studies by *Ahn et al[33].* , which included studies published up until June 2012 on the use of H2RAs or proton pump inhibitors (PPIs) and the risk of gastric cancer. In addition, La Vecchia and Tavani 2002[34] summarized many of the original case reports and initial studies from the 1970s, 1980s and 1990s. Additionally, studies by García Rodríguez 2006[35], Poulsen et al. 2009 [36] and Brusselaers et al. 2017 [37] addressed further protopathic bias, as well as the challenges of H2 receptor antagonists being available by prescription and over the counter.

The data provided underscore the challenges to adequately adjust for underlying indications, potential protopathic bias as well as the potential for associations with differing by type of gastric cancer and underlying co-morbidities (*e.g. H. pylori* infection).

The data arising from epidemiological studies is scarce mainly due to the challenges of performing such studies with interpretable and meaningful results. The primary objective of such studies should be to measure the overall cancer incidence rate (excluding non-melanoma skin cancer), and the incidence rate of specific cancer types, including renal cancer, bladder cancer, lung cancer, breast cancer, testis cancer, ovarian cancer and gastro-intestinal cancers (oesophageal cancer, gastric cancer, pancreatic cancer, liver cancer, gallbladder cancer, colorectal cancer) in a patient population. These should exclude any prior diagnosis of cancer and with at least two weeks of exposure in the following exposure groups:

  i.   new incident users of ranitidine

  ii.   new incident users of any substance of the H_2-receptor antagonist group

  iii. new incident users of any substance in the PPI group (excluding patients previously exposed to a H_2-receptor antagonist)

These studies should have at least a minimum of 1 year of data availability prior to first substance exposure, a lag time of 1 year between exposure and outcome, a minimum duration of follow-up after the first prescription of the concerned substance (to be proposed), a minimum duration of treatment of

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[33] Ahn JS, Eom C, Jeon CY, Park SM. Acid suppressive drugs and gastric cancer: A metaanalysis of observational studies. World Journal of Gastroenterology 2013 04;19(16):2560-2568.
[34] La Vecchia CL, Tavani A. A review of epidemiological studies on cancer in relation to the use of anti-ulcer drugs. European Journal of Cancer Prevention 2002;11(2):117-123.
[35] García Rodríguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. Gut 2006; 55:1538-1544
[36] Poulsen AH, Christensen S, McLaughlin JK et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 2009;100:1503–7.
[37] Brusselaers N, Wahlin K, Engstrand L, Lagergren J. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ open 2017 Oct 30;7(10):e017739.

two weeks. Age-standardised rates by gender (with confidence intervals) should be presented for each exposure group and, where appropriate, stratified for different cumulative exposures or different cumulative treatment durations.

There should also be a measure of the association between ranitidine exposure and the risk of occurrence of cancer, excluding non-melanoma skin cancer, as described in objective 1, in comparison to:

   i.   Patients exposed to all substances of the class (except ranitidine)

   ii. Patients exposed to PPIs but not to H_2-receptor antagonists.

This comparison should take into account the risk of protopathic bias and relevant potential confounding factors including, if feasible, smoking, obesity, diabetes, socioeconomic status and presence of helicobacter pylori. Relative risk estimates should be stratified by type of cancer and cumulative exposures or different cumulative treatment durations.

Most of the databases do not include such a complete subset of information making such study designs extremely challenging to implement, hence the lack of this type of observational studies data.

The available studies, despite their limitations, do not indicate an association between cancer and administration of H2-receptor antagonists.

2.5.3. Discussion on clinical aspects

Based on a comprehensive review of epidemiological and post marketing data currently available, it can be concluded that there is no evidence of a causal association between ranitidine therapy and the development of cancer in patients. 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, post marketing reporting or epidemiological studies.

Notwithstanding the above, it is clear the underlying disease increases the risk for gastric and pancreatic cancers in patients treated with H_2-receptor antagonists (this is also observed for patients treated with PPI[38,39]). Therefore, it is assumed that this association is an artefact of indication bias, among other confounders. Other important limitations are lack of adjustment for important confounders and limited sample size.

The (theoretical) excess cancer risk over lifetime introduced by NDMA might be extrapolated from the above-mentioned rat carcinogenicity study (Peto et al 1991). However, the risk in humans can only be appropriately estimated when ranitidine-related exposure to NDMA is known. The exogenous contribution by ranitidine use can be determined by measuring NDMA concentrations in the drug products. For the potential endogenous formation of NDMA additional *in vivo* data in humans would be needed, since the available data are inconclusive.

Data showed that after IV administration of 150 mg ^{3}H-ranitidine 93% was excreted in urine, of which 70% was unchanged parent drug (i.e. not metabolised). This contrasts with the level of excretion in urine after oral administration of 150 mg ^{3}H-ranitidine which is of 70% of which 35% was unchanged parent drug. It was argued that the potential for *in vivo* formation of nitrosamine might be of less concern in view of lower level of metabolization (this route of administration may not expose patients to NDMA formation from ranitidine due to gastric fluids or gastrointestinal microflora).

[38] M. Kearns, B Boursi and Yu-Xiao Yang, Proton pump inhibitors on pancreatic cancer risk and survival. Cancer Epidemiol. 2017 Feb; 46: 80–84.
[39] Ka Shing Cheung and Wai K. Leung. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. Therap Adv Gastroenterol. 2019; 12: 1756284819834511

The observed differences between oral and parenteral administration may reflect first-pass metabolism and/or metabolism by the intestinal flora. Although the quantity of ranitidine metabolized is lower after parenteral administration, it is still uncertain whether less NDMA will be formed from ranitidine (if endogenous formation indeed occurs). It would depend on the site of formation. If the potential site of formation is gastrointestinal, then indeed the concern would be much less after parenteral administration. If, however, NDMA is a product of renal metabolism this is not likely the case and considering the higher rate of renal excretion after parenteral administration, the quantity of NDMA formed could even be higher.

The CHMP also considered that an LTL approach for ranitidine containing products would not justify setting higher limits in view of the risks of NDMA and benefits of ranitidine, but also that the use might be repeated or be chronic.

MAHs have argued that the solutions for injection/infusion are only used for a limited time (less than 1 year) and the maximum daily dose for the parenteral forms is lower than for the tablet form (maximum daily dose (MDD) suggested 350 mg based on an average body weight of 50 kg), and therefore a higher limit for NDMA content might be considered (3.65 ppm), and that all parenteral products, for which data have been provided, would comply with this limit of 3 ppm (highest level observed <1.3 ppm). Nevertheless, the CHMP did not agree that the LTL approach could be applied either for parenteral ranitidine products for the reasons outlined above. The maximum daily dose is however lower in parenteral compared to oral dosage forms, which may lead to a higher limit (in terms of ppm per amount of active substance) applicable for parenteral forms.

3. Benefit-risk balance

3.1. Initial benefit-risk balance assessment

Benefits

Efficacy of H_2-receptor antagonists for the treatment of acid-related disorders is well-known. In a Cochrane review by Sigterman et al. (2013)[40] the risk ratio for heartburn remission for H_2-receptor antagonists compared to placebo treatment was 0.77 (95% CI: 0.60 - 0.99) (2 studies, n= 1013). Similar results were obtained for the comparison between these treatments concerning endoscopy negative reflux disease (risk ratio 0.84 (95% CI 0.74 - 0.95)) (2 studies, n= 514). In respective Cochrane review, similar trends in effects for H_2-receptor antagonists compared to placebo treatment as empirical treatment for gastro-oesophageal reflux disease were also observed with respect to other endpoints such as overall symptom improvement (risk ratio 0.72 (95% CI: 0.63 - 0.81)), daytime heartburn relief (risk ratio 0.80 (95% CI : 0.71 - 0.89)), and night time heart burn relief (risk ratio 0.77 (95% CI : 0.63 - 0.94)). Studies in which the clinical effects of ranitidine were evaluated, were included in the aforementioned Cochrane review (Sigterman et al. (2013)).

Because of the demonstrated efficacy of H_2-receptor antagonists, international treatment guidelines indicate that H_2-receptor antagonists may be used for the treatment of acid-related disorders (e.g. World Gastroenterology Organisation (Hunt et al. 2017) [41], European Association of Endoscopic Surgery (Fuchs et al. 2014[42])). It is however acknowledged that efficacy of H_2-receptor antagonists is

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[40] Sigterman et al., Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease: Cochrane Systematic Review - Intervention Version published: 31 May 2013
[41] Hunt R. et al., World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease - J Clin Gastroenterol. 2017 Jul;51(6):467-478. doi: 10.1097/MCG.0000000000000854.
[42] Fuchs K.H. et al., EAES recommendations for the management of gastroesophageal reflux disease.Surg Endosc. 2014 Jun;28(6):1753-73. doi: 10.1007/s00464-014-3431-z. Epub 2014 May 2.

considered uncertain according to current guidelines on paediatric gastroesophageal reflux of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (Rosen et al. 2018 [43]).

It is also acknowledged that proton pump inhibitors were shown to be more effective than ranitidine and other H_2-receptor antagonists for the treatment of gastroesophageal reflux disease (Sigterman et al. 2013; MacFarlane 2018 [44]; Rosen et al. 2018).

Risks

Adverse drug reactions of ranitidine are seldomly observed (i.e. 1/10.000 or less) (product information ranitidine product Zantac). Observed adverse drug reactions include hypersensitivity reactions, leukopenia, thrombocytopenia, reversible confusion, depression, dizziness, hearth rhythm disturbances (bradycardia, AV-block, tachycardia), and diarrhoea.

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 IARC as "probably carcinogenic to humans" (Class 2A carcinogen).

The impact of NDMA on human health is currently only extrapolated from animal studies. However, as the DNA damage mechanisms documented in these studies are also relevant in humans and *in vitro* data in human cells are not significantly different from those in animal cells, it is prudent to assume that effects seen in animals may also occur in humans after exposure to sufficiently large amounts of this nitrosamine. Additional exposure to NDMA due to treatment with ranitidine when containing NDMA as impurity, or leading to additional endogenous formation of NDMA, should be seen as an additional risk factor adding to the total tumour risk associated with nitrosamine exposure.

NDMA is not only present in ranitidine finished products as an impurity that may form during the manufacturing process. It also appears to increase over time as a consequence of degradation and has been found in the majority of tested batches above the daily exposure to NDMA of 96 ng, which has previously been set as Acceptable Intake (AI) considering lifetime exposure. Furthermore, due to a lack of sufficient information, a possible endogenous formation of NDMA arising from ranitidine cannot be excluded.

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 addition, in view of the presence of NDMA in the drug substance and product, the formation of NDMA as a degradation product and the uncertainties related to the risk of *in vivo* formation as well as its extent, the CHMP did not identify risk minimisation measures that could minimise the risk to an acceptable level at this stage. Thus, CHMP considers that avoiding the use of ranitidine containing products until the above uncertainties are addressed is the only acceptable risk minimisation measure.

In the absence of reliable data on the extent of NDMA exposure in patients treated with ranitidine contaminated with NDMA, it is also not possible at this stage to fully assess the cancer risk in these patients. While epidemiological or clinical trial data so far did not indicate an increased risk of cancer in

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[43] Rosen R. et al, Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition.J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516-554.
[44] MacFarlane B, Integr Pharm Res Pract. 2018 Jun 5;7:41-52. doi: 10.2147/IPRP.S142932. eCollection 2018. Management of gastroesophageal reflux disease in adults: a pharmacist's perspective.

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.

Conclusion

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.

3.2. Re-examination procedure

On 3 June 2020, S.A.L.F. S.p.A. Laboratorio Farmacologico (further stated as S.A.L.F. in this report) - as the MAH of Ranitidina S.A.L.F. 50 mg/5 ml, nationally authorized in Italy, requested a re-examination of the CHMP opinion on Ranitidine-containing medicinal products according to Article 32(4) of Directive 2001/83/EC.

The CHMP is a scientific committee and therefore this re-examination procedure has focused only on the scientific grounds as raised by SALF.

3.2.1. Detailed grounds for re-examination submitted by the applicant/MAH

Detailed grounds for re-examination have been submitted by the MAH on 29 July 2020 and are primarily focused on the LTL approach and measures to limit the exposure to NDMA.

The SmPC of the Ranitidine S. A. L. F. 50 mg/5 ml solution for injection presented in the dossier states that the treatment is limited to short periods and should be administered under close medical supervision. Ranitidine can be administered parenterally either as an intravenous injection of 50 mg repeatable every 6-8 hours or as an intermittent intravenous infusion. In this case the normal dose is 25 mg / hour for 2 hours and can be repeated at 6-8-hours intervals.

In the prophylaxis of stress ulcer haemorrhage in severely ill patients or recurrent haemorrhage in patients with bleeding peptic ulcer, a starting dose of 50 mg slow intravenous followed by continuous intravenous infusion of 0.125-0.250 mg / kg. In the prevention and treatment of stress ulcers in severely ill patients, the initial treatment is 50 mg intravenously 3-4 times a day.

In patients with severe renal impairment (creatinine clearance less than 50 ml / min), accumulation of ranitidine occurs with consequent increase in plasma concentrations. A daily dose of 25 mg for these patients is recommended

For upper gastrointestinal bleeding, treatment can be initiated with a 50 mg vial of ranitidine intravenously 3 or 4 times a day.

In premedication under anaesthesia, those patients who are at risk of developing acid aspiration syndrome (Mendelson's syndrome) may be given a 50 mg vial of Ranitidine S.A.L.F. by slow IV injection 45 to 60 minutes prior to induction of general anaesthesia.

In children (6 months to 11 years) Ranitidina S.A.L.F. Solution for injection can be administered by slow intravenous injection (over 2 minutes) up to a maximum of 50 mg every 6-8 hours. For the acute treatment of peptic ulcer and gastroesophageal reflux in paediatric patients, Ranitidine S.A.L.F. Solution for injection can be administered at doses that have been shown to be effective in these conditions in adults and effective in acid suppression in severely ill children. The starting dose (2.0 mg / kg or 2.5 mg / kg, maximum 50 mg) can be given as a slow intravenous infusion for over 10 minutes, or with a syringe followed by 3 ml of normal saline for over 5 minutes, or following dilution with normal saline to 20 ml. Maintenance of pH > 4.0 can be achieved by intermittent infusion of 1.5 mg / kg every 6-8 hours. Alternatively, treatment can be continuous, administering a loading dose of 0.45 mg / kg followed by a continuous infusion of 0.15 mg / kg / hour.

These indications result in a maximum daily dose of the product of 200 mg of ranitidine per day, with the exception of the prevention of Mendelson's syndrome, where a single 50 mg dose is given prior to surgery.

LTL approach to set NDMA limit in ranitidine-containing parenteral formulations

The MAH highlighted that when the NDMA limit set by the CHMP (set at 96 ng/day (ng/mg)) is applied taking into account the maximum daily dose of Ranitidina S.A.L.F. 50 mg/5 ml (200 mg equal to 4 glass ampoules), the maximum limit for NDMA would then be 0.48 ppm (ng/mg) which corresponds to 4.8 ng/ml or 24 ng/ampoule.

The analytical results from the MAH's batches submitted during the referral procedure (expired batches and other which run to expiry date) show that the obtained values are above this limit.

However, if it is considered that the therapy - by using Ranitidine S.A.L.F. as solution for injection- is based on short-time period, the MAH claims that the following limits could be adopted according to the approach described in the ICH M7 guideline:

Duration	1 day - 1 month	1 month - 1 year	1 year - 10 years	10 years - lifetime
Daily intake ppm	80 X 0.48 = 38.40 ppm	13.3 X 0.48 = 6.38 ppm	6.7 X 0.48 = 3.22 ppm	1 X 0.48 = 0.48 ppm

On the basis of these daily intake values, the MAH claims that results obtained from analyses of NMDA on Ranitidina S.A.L.F. would be within the limits for 1 day / 1 month, 1 month / 1 year and in many cases for 1 year/ 10 years durations.

The MAH argued that the less than lifetime (LTL) approach as per ICH M7(R1) can be applied to the case of ranitidine since the AI derived for ranitidine (96 ng/day) is calculated for lifetime exposure and most patients will use ranitidine for only a limited period of time.

The MAH therefore requested to re-consider the limit of NDMA in relation to ranitidine administered by parenteral route and to apply the "less-than- lifetime" approach for these products due to the fact that the therapy with Ranitidina S.A.L.F. cannot be prolonged more than 1 month and that this medicine has been considered critical by the Italian national competent authority (AIFA).

Measures to minimise the exposure

The MAH argued, that should the CHMP not agree with the applicant's position on NDMA limits, the MAH could agree to restrict the authorised therapeutic indications for their ranitidine-containing parenteral products to the anaesthesia premedication in those patients who risk developing an acid aspiration syndrome (Mendelson syndrome). In this case, since it is a single administration, the MAH claimed that the nitrosamine content is irrelevant, and in view of an NDMA limit, the LTL approach for 1 day-1 month should be taken into account.

With regards to the potential endogenous formation of NDMA, the MAH claimed that the formation of nitrosamines is completely averted by the weak acidic or even alkaline pH and committed to participate in a study to investigate potential endogenous formation of NDMA in the kidney, taking into account the parenteral route of administration of ranitidine.

3.2.2. CHMP discussion 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."

3.2.3. Conclusion on the benefit-risk balance following the re-examination procedure

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.

4. Condition(s) to for lifting the suspension of the marketing authorisations

Proposed conditions to lift the suspension of the marketing authorisation Ranitidine Solution for Injection/Infusion **for single use only** are as follows:

Condition for lifting suspension
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.

For other ranitidine containing products, the following conditions for lifting a suspension should apply and for the suspension to be lifted, the Marketing Authorisation Holder(s) shall provide the following:

Condition for lifting suspension
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.

5. Grounds for 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.

The Committee, in view of the available data including the detailed grounds submitted by S.A.L.F. during the re-examination phase, considered that the benefit-risk balance of ranitidine containing medicinal products is not favourable.

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

The conditions imposed to lift the suspension of the marketing authorisations are set out in section 4 of this report.