12 November 2020
EMA/47245/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Impact of the Article 5(3) scientific opinion on nitrosamines in human medicinal products on the Opinion adopted pursuant to Article 31 of Directive 2001/83/EC for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan)

Procedure no: EMEA/H/A-31/1471

Nationally authorised products: various

Centrally authorised products:

Amlodipine-Valsartan Mylan EMEA/H/A-31/1471/C/4037/0004; Aprovel EMEA/H/A-31/1471/C/141/0172; Coaprovel EMEA/H/A-31/1471/C/222/0187; Copalia EMEA/H/A-31/1471/C/774/0099; Copalia HCT EMEA/H/A-31/1471/C/1159/0069; Dafiro EMEA/H/A-31/1471/C/776/0101; Dafiro HCT EMEA/H/A-31/1471/C/1160/0070; Entresto EMEA/H/A-31/1471/C/4062/0021; Exforge EMEA/H/A-31/1471/C/716/0098; Exforge HCT EMEA/H/A-31/1471/C/1068/0068; Ifirmacombi EMEA/H/A-31/1471/C/2302/0020; Ifirmasta EMEA/H/A-31/1471/C/962/0018; Irbesartan Hydrochlorothiazide Zentiva EMEA/H/A-31/1471/C/783/0101; Irbesartan Teva EMEA/H/A-31/1471/C/1093/0032; Irbesartan Zentiva EMEA/H/A-31/1471/C/785/0080; Irbesartan/Hydrochlorothiazide Teva EMEA/H/A-31/1471/C/1112/0041; Karvea EMEA/H/A-31/1471/C/142/0175; Karvezide EMEA/H/A-31/1471/C/221/0188; Neparvis EMEA/H/A-31/1471/C/4343/0020

Active substances: candesartan, irbesartan, losartan, olmesartan, valsartan

Note:

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

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1. Information on the procedure

As part of the assessment of the Art. 31 referral procedure for sartans with a tetrazole ring, the CHMP recommended that the conditions for sartans with a tetrazole ring should be reviewed to take into account the recommendations from the Art. 5(3) on nitrosamines. On 29 July 2020 the EC sent a letter to EMA requesting the assessment of the impact of the outcome of the Article 5(3) assessment on nitrosamines adopted on 25 June 2020 on the CHMP opinion of 31 January 2019 for the scientific assessment and review under Article 31 of Directive 2001/83/EC regarding angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471).

The scope of this procedure is limited to medicinal products containing sartans with a tetrazole ring.

2. Scientific discussion

2.1. Introduction

In a letter dated 29 July 2020, the European Commission requested EMA to assess the impact of the outcome of the Article 5(3) assessment on nitrosamines adopted on 25 June 2020 on the CHMP opinion of 31 January 2019 for the scientific assessment and review under Article 31 of Directive 2001/83/EC regarding angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471).

The EC further asked if it is concluded that there is a need to review the recommendation which was given in 2019, this should be fully explained in a self-standing detailed opinion, including the scientific conclusions and grounds for the updated advice, including an assessment on the need to change the conditions to the marketing authorisations of angiotensin-II-receptor antagonists (sartans) medicines containing a tetrazole group.

The CHMP confirmed during its September 2020 plenary meeting that the outcome of the Article 5(3) review on nitrosamine is relevant for the aforementioned Art. 31 referral on sartans with a tetrazole group and the Rapporteurs of the sartans referral were asked to provide an assessment on the matter.

2.2. Article 31 referral procedure on sartans with a tetrazole ring

EU authorities were notified in June 2018 that an Active Pharmaceutical Ingredient (API) manufacturer (Zhejiang Huahai Pharmaceutical, China) had detected the presence of a previously undetected impurity, N-nitrosodimethylamine (NDMA, also known as dimethylnitrosamine) in the valsartan API manufactured at its site in Chuannan. Zhejiang Huahai is one of the API manufacturers that are supplying valsartan for medicinal products authorised in the EU.

NDMA is a genotoxic and carcinogen agent in animals and it is classified as a probable human carcinogen by IARC (International Agency for Research on Cancer, WHO).

An initial investigation report on the root cause of the presence of NDMA by the manufacturer indicates that NDMA formed at a specific step in the valsartan API manufacturing process, and the level of NDMA present may depend on the reaction conditions used.

The European Commission triggered on 5 July 2018 a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of nitrosamine impurities on the benefit-risk balance of

valsartan-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

During the CHMP plenary meeting in September 2018, the scope of the referral has been widened to include all sartans with a tetrazole group in their molecular structure (candesartan, irbesartan, losartan, olmesartan and valsartan).

Taking into account the available data, the CHMP considered in its opinion adopted on 14 February 2019 that the benefit risk balance of medicines containing a sartan with a tetrazole ring remains positive subject to the conditions outlined below. The CHMP opinion was forwarded to the European Commission, which issued final legally binding decisions for the medicines concerned between 2 April and 17 April 2019 that are applicable in all EU Member States.

The marketing authorisation holder(s) shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

<table>
<tr><th>Conditions to the MA</th><th>Due date</th></tr>
<tr><td>The MAH must ensure that the manufacturing processes of the drug substances used for their drug products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible.</td><td>Within 2 years after Commission Decision.</td></tr>
<tr><td>For all N-nitrosamines, the MAH must ensure a control strategy is in place in drug substance batches used for their drug products.</td><td>At the time of Commission Decision.</td></tr>
<tr><td>For N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), the MAH must introduce the following specifications for the drug substance:

1) Limits for NDMA and NDEA outlined below should be implemented for a transitional period of 2 years:
<table>
<tr><th>Drug substance*</th><th>Max. daily dose (mg)</th><th>NDEA Limit in ng/day</th><th>NDEA Limit in ppm in API</th><th>NDMA Limit in ng/day</th><th>NDMA Limit in ppm in API</th></tr>
<tr><td>Valsartan</td><td>320</td><td>26.5</td><td>0.082</td><td>96.0</td><td>0.300</td></tr>
<tr><td>Losartan</td><td>150</td><td>26.5</td><td>0.177</td><td>96.0</td><td>0.640</td></tr>
<tr><td>Olmesartan</td><td>40</td><td>26.5</td><td>0.663</td><td>96.0</td><td>2.400</td></tr>
<tr><td>Irbesartan</td><td>300</td><td>26.5</td><td>0.088</td><td>96.0</td><td>0.320</td></tr>
<tr><td>Candesartan</td><td>32</td><td>26.5</td><td>0.820</td><td>96.0</td><td>3.000</td></tr>
</table>
* These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.

2) After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.</td><td>At the time of Commission Decision

Within 2 years after Commission Decision.</td></tr>
</table>

Some marketing authorisation holders have already implemented the conditions imposed in 2019 and updated the terms of the marketing authorisation to take this into account.

In June 2020, the European medicines regulatory network published the outcome of a lessons learned exercise on the presence of nitrosamines in sartan medicines. This includes recommendations to

help reduce the risk of impurities in medicines and ensure that regulators are better prepared to manage cases of unexpected impurities.

2.3. Article 5(3) scientific opinion on nitrosamines in medicinal products for human use

Building on the Article 31 referral on sartans with a tetrazole ring and the knowledge acquired on N-nitrosamines in medicinal products, EMA together with the EU Network and international partners has continued the review of medicinal products to identify if there are any risks of nitrosamine presence outside the class of sartans.

Taking into account that N-nitrosamines have been found in sartans with a tetrazole ring but also in other API/medicinal products (e.g. in some batches of pioglitazone and ranitidine) on 10 September 2019 the EMA's Executive Director initiated a procedure under Article 5(3) of Regulation EC (No) 726/2004, and requested the CHMP to further investigate the issues at stake and to give a scientific opinion on

- considerations for MAHs for medicinal products for human use containing chemically synthesised active pharmaceutical ingredients on the identification of the possible presence of N-nitrosamine impurities in their medicinal products ("call for review"); and
- all available scientific knowledge on N-nitrosamine impurities in human medicines containing chemically synthesised active pharmaceutical ingredients and their impact on the safe use of medicines. In this exercise the CHMP could seek the support of additional experts and stakeholders as needed. Such evaluation should include the need whether or not to broaden the scope, in a next phase, to products other than human medicines containing chemically synthesised active pharmaceutical ingredients.

Based on the assessment of all available data and consultations with external experts, PRAC, and Working Parties, the CHMP adopted on 25 June 2020 the following recommendations in its opinion under Article 5(3) of Regulation (EC) no 726/2004:

1. The presence of N-nitrosamines in human medicinal products shall be mitigated as much as possible and shall be at or below a limit based on ICH M7(R1) principles for substances of the "cohort of concern" defined in this guideline and calculated considering a lifetime daily exposure.

   This should be achieved by an appropriate control strategy and by the design or adaptation of the manufacturing processes aiming to prevent formation of and contamination with nitrosamines whenever possible.

2. The risk of presence of nitrosamines must be evaluated by the MAHs/Applicants. In case of risk, confirmatory testing must be performed.
   - A risk evaluation/risk assessment for the presence of nitrosamines must be submitted for new marketing authorization applications at the time of submission, and for already authorized medicinal products containing chemically synthesised active pharmaceutical ingredients (APIs) as per the 'call for review'[1] and for biological medicinal products in a similar exercise as per instructions to be published in a Questions and Answers document[2].

[1] https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf
[2] https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf

- The approach for risk evaluation/risk assessment should cover manufacturing processes of active substance and finished product in consideration of the root-causes, and subsequent confirmatory testing in the finished product, in case a risk is identified.
- Although the overall risk of presence of nitrosamines in biological medicinal products is considered very low, the following risk factors should be taken into consideration: biologicals containing chemically synthesized fragments, where risk factors similar to chemically synthesized active substances are present, biologicals using processes where nitrosating reagents are deliberately added, or those packaged in certain primary packaging material, such as blister packs containing nitrocellulose.

3. Where a nitrosamine has been detected, a limit based on the above-mentioned ICH M7(R1) principles for "cohort of concern" substances considering a lifetime daily exposure should be calculated.

   The following limits have been established for some specific N-nitrosamines and should be applied:

***N*-Nitrosamine (CAS number)**	**ng/day*** **
NDMA* (62-75-9)	96.0
NDEA*(55-18-5)	26.5
EIPNA**(16339-04-1)	26.5
DIPNA**(601-77-4)	26.5
NMBA**(61445-55-4)	96.0
MeNP**(16339-07-4)	26.5
NDBA**(924-16-3)	26.5

   These limits are applicable only if a finished product contains a single N-nitrosamine.

   * Limit calculated on the basis of harmonic mean TD_{50} derived from carcinogenic potency database (CPDB)

   **Limit derived using SAR/read-across approach

   ***The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective above limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC.

   - The limit as calculated above will usually need to be included in the finished product specification.
   - Skip testing is only justified if it can be shown that the levels of the respective nitrosamine are consistently ≤ 30% of the limit defined above and the root cause is identified and well-understood.
   - Omission from the specification is only justified if it can be shown that the levels of the respective nitrosamine are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood.

4. If more than one N-nitrosamine is identified in a given finished product (or its API), it must be

ensured that the total risk level of the sum of all detected N-nitrosamines does not exceed 1 in 100,000 life-time risk. An alternative approach where the sum of all detected N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified may also be used. The approach chosen for a particular case needs to be duly justified by the applicant/MAH.

5. Exceptionally, when a single N-nitrosamine cannot be kept below the limit defined in 3. or the total risk level of the sum of more than one detected N-nitrosamine cannot be kept below a 1 in 100,000 life-time risk, the MAH should submit to the relevant competent authorities forthwith an investigation report including the potential/identified root cause(s), preventive/corrective actions and a thorough discussion on the impact on the benefit/risk balance including all relevant considerations (e.g. medical need, daily dose, duration of administration and treatment alternatives, potential patient risk in case of drug shortage). Acceptability of limits higher than those defined in 3 and 4. is then decided by the relevant competent authorities on a case-by-case basis, after having performed a benefit/risk evaluation. In such instances, the "less-than-lifetime" (LTL) concept in ICH M7(R1) may be considered by the competent authorities for the range of a temporarily acceptable exposure until further measures can be implemented to reduce the contaminant at or below the limits defined in point 3 and 4.

6. Exceptions to sections 3 and 4 include some products falling outside the scope of the ICH M7(R1) guideline, i.e. certain active substances and finished products intended for advanced cancer indications or when the active substance is itself genotoxic. For finished products intended only for advanced cancer, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2), as specified in the Q&A document to ICH S9. When the active substance itself is genotoxic at therapeutic concentrations, N-nitrosamine impurities could be controlled at limits for non-mutagenic impurities according to ICH M7(R1).

7. When N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data to calculate a reliable TD_{50} then this should be used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R1).

8. When *N*-nitrosamines are identified with insufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R1), a class specific Threshold of Toxicological Concern (TTC) for nitrosamines of 18 ng/day can be used as default option. This TTC has been derived from the Lhasa carcinogenic potency database and is considered a conservative and acceptable approach. If a MAH intends using a higher limit than 18 ng/day, an approach based on structure-activity-relationship (SAR) considerations is acceptable. The approach taken needs to be duly justified by the applicant/MAH.

9. MAHs should implement a control strategy regarding N-nitrosamines for their active substances and finished products, 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 related to the premises and equipment e.g. cleaning procedures, environmental monitoring,…) and control any future change that may impact on this risk (e.g. change of supplier, change of manufacturing process, change of packaging…)

   In order to fulfil their obligations above, MAH/applicants shall:

   - carry out risk evaluation/risk assessment of manufacturing processes of API (route of synthesis, starting materials, intermediates, raw materials) in view of potential formation of or contamination with N-nitrosamines, taking into account potential and confirmed root causes for the presence of N-nitrosamines in APIs.

- carry out risk evaluation/risk assessment of finished product (degradation of API, primary packaging material, excipients, etc.), taking into account the root-causes for the presence of *N*-nitrosamines in finished products.
- ensure that, in accordance with Article 23 and Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, their medicinal products are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, MAHs/Applicants shall design their manufacturing processes and controls to prevent if possible or mitigate as much as possible the presence of *N*-nitrosamines in their API and finished product(s) and shall introduce any subsequent changes to their manufacturing process as needed.
- ensure that active substances and excipients used in their finished products are manufactured in compliance with good manufacturing practices as laid down in Article 46(f) of Directive 2001/83/EC.
- MAHs'/Applicants' compliance with the above-mentioned obligations is subject to regular controls by competent authorities including during inspections.

10. With regard to the analytical method(s) employed the following is advised:
    - The limit of quantitation (LoQ) provides the minimum level at which an analyte can be quantified with acceptable accuracy and precision and should thus be used to define the required analytical sensitivity for impurity testing.
    - If quantitative testing is performed as a routine control, the LoQ should be at or below the limit for the respective nitrosamine impurity defined in 3.
    - If quantitative testing is performed to justify skip testing, the LoQ of the analytical procedure employed should be ≤ 30% of the limit defined in 3.
    - If quantitative testing is performed to justify omission of specification, the LoQ of the analytical method employed should be ≤ 10% of the limit defined in 3.
    - Higher sensitivity of analytical methods may be needed for medicinal products used at high daily doses or in case more than one nitrosamine is anticipated or identified in a given medicinal product. Such cases should be discussed with the relevant competent authority/ies.
    - Different analytical methods may be used for determination of multiple nitrosamines. If the same analytical method is used for multiple nitrosamines, the selectivity of the method should be demonstrated at the LoQ for each nitrosamine.
11. Although further epidemiological studies would be useful to better characterize the relationship between nitrosamine exposure from medicinal products and cancer risk, critical challenges have been identified such as large sample size, long study duration, determination of exposure, identification of confounding factors and adequate control group which would be necessary to achieve meaningful and interpretable results. Nationwide registries or large healthcare database might be the most promising approach but may not contain all important information. In such cases, data linkage to other data sources that may contain the missing information should be checked prior to study initiation. Furthermore, the possibility of a meta-analytical approach may be considered in case of insufficient patient numbers in a given data source.

3. Assessment of the impact of the outcome of the Article 5(3) assessment on the CHMPs opinion of 31 January 2019 for the scientific assessment and review under Article 31 of Directive 2001/83/EC regarding angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471)

Based on the knowledge acquired on the presence of nitrosamines in medicinal products since the sartans referral and taking into account the data assessed within the Art 5(3) review, in particular related to the methodology to calculate the limits in case of (poly)contamination and potential root causes, the CHMP considered that the outcome of the sartans referral should be amended to take into account the outcome of the Art. 5(3) review. Having considered that the sartan case is well characterised and the API processes were identified as the main and often only root-cause, the CHMP is of the view that there is no specific aspect that would warrant a general exception for sartans with a tetrazole ring.

In the Art 5(3) review, the CHMP did not support the approach to control nitrosamines based on analytical capability (i.e., technical limit applied at active pharmaceutical ingredient level), as this does not take into account toxicological data, and limits may be different for different nitrosamines. Furthermore, it could lead to different actual exposures depending on the daily dose of the medicinal product. Nitrosamines should also be controlled usually at the level of the finished product, as several root causes emerged that are related to finished product manufacturing. The control point for nitrosamines should be selected in such a way that it will give assurance of presence of the impurity below the acceptable limit in the finished product.
The CHMP considers that those recommendations adopted in the Art 5(3) review are also relevant to sartans with tetrazole ring as follows, with the below rationale added.

3.1. Limits for nitrosamines applicable if a drug product contains a single N-nitrosamine

The CHMP agrees that the limits for finished products for NDMA, NDEA, N-nitrosoethylisopropylamine (EIPNA), N-nitrosodiisopropylamine (DIPNA), N-methyl-4-aminobutyric acid (NMBA), 1-nitroso-4-methyl piperazine (MeNP) and N-Nitrosodibutylamine (NDBA) mentioned in the Art.5(3) assessment report (see table below) and limits for further nitrosamines reflected in the Q&A on nitrosamines (EMA/409815/2020) should apply also for the finished products containing sartans with a tetrazole ring, in case their formation can be expected based on the risk assessment.

***N*-Nitrosamine (CAS number)**	**ng/day**
NDMA (62-75-9)	96.0
NDEA (55-18-5)	26.5
EIPNA (16339-04-1)	26.5

DIPNA (601-77-4)	26.5
NMBA (61445-55-4)	96.0
MeNP (16339-07-4)	26.5
NDBA (924-16-3)	26.5

In view of the multiple potential sources of contamination with nitrosamines, the CHMP considers that these limits should be applied to the finished sartan products in line with the Art. 5(3) recommendation instead of the API only, as is currently requested. In addition, the same control strategies and testing modalities as described in the Art.5(3) report should apply.

Consequently, the limits requested as part of the Conditions to the Marketing authorisations need to be amended accordingly.

By analogy, the below recommendations apply for sartans with a tetrazole ring:

- When *N*-nitrosamines other than the above are identified with sufficient substance specific animal carcinogenicity data to calculate a reliable TD_{50} this should be used to derive a substance specific AI for lifetime exposure as recommended in ICH M7.

- When *N*-nitrosamines are identified with insufficient substance specific toxicological data to derive a substance specific AI, based on the Art 5(3) assessment, a class specific TTC for nitrosamines of 18 ng/day can be used, which has been derived from the Lhasa carcinogenic potency database and is considered a conservative and acceptable approach. If a MAH intends using a higher limit, an approach based on SAR considerations is acceptable. This approach should adhere to the principles also outlined in the Art 5(3) assessment report and needs to be duly justified by the applicant/MAH.

3.2. Limits in the case of presence of more than one nitrosamine

While the Art. 31 referral for sartans did not allow simultaneous nitrosamine contaminations in the same API, the CHMP considered as part of the Art 5(3) review that two approaches for determining limits in the case of presence of more than one nitrosamine are considered acceptable in order not to exceed the acceptable 1:100,000 additional risk level as outlined in ICH M7(R1):

1. The sum of all identified *N*-nitrosamines not to exceed the AI of the most potent *N*-nitrosamine identified, or

2. Total risk level of the sum of all detected *N*-nitrosamines not to exceed 1 in 100,000.

The approach chosen for a particular case needs to be duly justified by the applicant/MAH.

As the levels in the finished product will be kept below a 1:100,000 excess lifetime risk (as with single contaminations), the CHMP considers that the above approach is also considered acceptable for sartans.

Exceptionally, when the presence of a single or more than one N-nitrosamine cannot be kept at or below the above limit/an excess lifetime risk of 1:100,000 despite adequate process development and an adequate control strategy, a thorough benefit/risk assessment including all relevant considerations (e.g. medical need, daily dose, duration of administration and treatment alternatives, potential patient

risk in case of drug shortage) should be submitted to the relevant competent authorities. Acceptability of limits higher than the above limits is then decided by the relevant competent authorities on a case-by-case basis.

3.3. Testing modalities

The CHMP considers that the recommendations on analytical method(s) employed would also be applicable to the sartans with a tetrazole ring as with any other medicinal product as with the knowledge gained in the Article 5(3) review there is no rational that could justify that these recommendations would not apply to sartans with tetrazole ring. The following testing modalities should therefore apply, and the conditions need to be revised accordingly:

- If a risk has been identified for the finished product manufacturing or nitrosamines have been detected in the finished product but the actual source or the stage at which the contamination enters the process is unclear, a routine test of the finished product is expected.

  The limit will usually need to be included in the finished product specification as recommended in the Art 5(3) procedure. In the case of sartans, this means that the specification will need to be set for the finished product instead of the API, however, if duly justified the control point for nitrosamines can be selected in such a way that it will give assurance of presence of the impurity below the limit in the finished product.

- With regard to the analytical method(s) employed the following is advised:
  - If quantitative testing is performed as a routine control, the LoQ should be ≤ the relevant limit based on the principles of ICH M7 for cohort of concern substances (referred to as acceptable intake (AI) in the guideline) for the respective nitrosamine impurity.
  - Different analytical methods may be used for determination of multiple nitrosamines. If the same analytical method is used for multiple nitrosamines, the selectivity of the method should be demonstrated for each nitrosamine.
  - If quantitative testing is performed to justify skip testing, the LoQ of the analytical procedure employed should be ≤ 30% of the limit.
  - If quantitative testing is performed to justify omission of testing, the LoQ of the analytical method should be ≤ 10% of the limit.

3.4. Impact on Sartans Conditions

Overall, The CHMP considered that there is no specific aspect that would warrant a general exception for sartans with a tetrazole ring, and agreed moving the NDMA and NDEA specifications from the active substance to the finished product, with a limit according to ICH M7 principles for cohort of concern substances for lifelong exposure. In addition, the Art 5(3) recommendations on multiple nitrosamine contaminations, omission of testing and the option of skip testing are also applicable. A condition is included in order to request MAHs to adapt the current modalities of the NDMA/NDEA testing to the modalities defined in the Article 5(3). The MAHs have the opportunity as part of the implementation of this condition to request omission of the specification on the finished product or skip testing if justified and based on evidence. Should the MAHs not have sufficient evidence at this stage to request omission

of the specification or skip testing, this could be requested at later stage once the necessary evidence is available.

In general, the risk assessment and implementation of the mitigation measures for finished products sartans with a tetrazole ring can follow the timelines of the call for review for products containing chemically manufactured active substances, considering the effort needed to fully elucidate any potential risks and carry out testing, e.g. for other nitrosamines. The deadline for the conduct of the risk assessment and implementation of mitigation measures for the active substance is maintained, i.e. two years following initial Commission Decision, as it can be expected that MAHs have already progressed fulfilling or have already fulfilled this condition.

Based on the above scientific considerations, the outcome of the Art. 31 sartans referral should be aligned with the outcome of the Art. 5(3) review. Thus, the following highlighted changes to the current conditions to the MAs for sartans imposed in the context of the Article 31 referral procedure for these products, are recommended:

Conditions to the MA	**Due date**
The MAH must ensure that the manufacturing processes of the ~~drug~~ active substances used for their ~~drug~~ finished products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products (Article 5(3) procedure).	~~Within 2 years after Commission Decision~~ 17 April 2021
The MAH must ensure that the manufacturing processes of the finished product is reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation EC (No) 726/2004 on Nitrosamines impurities in human medicinal products.	26 September 2022
For all N-nitrosamines, the MAH must ensure a control strategy is in place for ~~drug~~ active substance batches used for their ~~drug~~ finished products possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation EC (No) 726/2004 on Nitrosamines impurities in human medicinal products (Article 5(3) procedure).	~~At the time Commission Decision~~ 17 April 2019 (last date of the Commission decisions related to the Article 31 referral adopted in 2019[3])
1/ For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications ~~for the drug substance~~: ~~1)~~Limits for NDMA (96 ng/day) and NDEA (26.5 ng/day)~~outlined below~~ should be implemented ~~for a transitional period of 2 years~~ for the finished product. The limit	~~At the time of Commission Decision~~ 30 June 2021

[3] Commission Implementing Decision C(2019)3157 (final) of 17.4.2019 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisation granted by Decision C(2016)1906(final) for "Amlodipine/Valsartan Mylan - amlodipine/valsartan", medicinal product for human use

should be calculated by dividing the respective limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC.

~~Drug substance*~~	~~Max. daily dose (mg)~~	~~NDEA Limit in ng/day~~	~~NDEA Limit in ppm in API~~	~~NDMA Limit in ng/day~~	~~NDMA Limit in ppm in API~~
~~Valsartan~~	~~320~~	~~26.5~~	~~0.082~~	~~96.0~~	~~0.300~~
~~Losartan~~	~~150~~	~~26.5~~	~~0.177~~	~~96.0~~	~~0.640~~
~~Olmesartan~~	~~40~~	~~26.5~~	~~0.663~~	~~96.0~~	~~2.400~~
~~Irbesartan~~	~~300~~	~~26.5~~	~~0.088~~	~~96.0~~	~~0.320~~
~~Candesartan~~	~~32~~	~~26.5~~	~~0.820~~	~~96.0~~	~~3.000~~

~~*These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.~~

The limit will usually need to be included in the finished product specification.

Omission from the specification is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood.

Skip testing is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 30% of the limits defined above and the root cause is identified and well-understood.

In accordance with the recommendations adopted on N-nitrosamines impurities in human medicinal products (Article 5(3) procedure), where the co-presence of the above N-nitrosamines has been identified in the same finished product, it must be ensured that the cumulative risk of these N-nitrosamines does not exceed a lifetime cancer risk (lifelong exposure) of 1:100,000. An alternative approach where the sum of these two N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified (NDEA) may also be used. The approach chosen for a particular case needs to be duly justified by the MAH.

The MAH shall ensure that the control strategy for all N-nitrosamines is updated accordingly.

~~After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.~~

~~Within 2 years after Commission Decision~~

4. Recommendations and next steps

Based on the review of all available data on safety and efficacy, the CHMP considers that the benefit-risk balance of medicinal products containing sartans with a tetrazole ring remains favourable and that the recommendations adopted in the nitrosamines Art 5(3) procedure are implemented also in the sartans with a tetrazole ring MA dossier.

Without prejudice to the following conditions, MAHs are reminded to follow the instructions of the call for review[4] for the assessment of the risk of presence of nitrosamines in their medicinal products and confirmatory testing if needed.

[4]https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities#guidance-for-marketing-authorisation-holders-section

Conditions to the MA(s) are varied as follows:

Conditions to the MA	**Due date**
The MAH must ensure that the manufacturing processes of the active substances used for their finished products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products (Article 5(3) procedure).	17 April 2021
The MAH must ensure that the manufacturing processes of the finished product is reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products.	26 September 2022
For all N-nitrosamines, the MAH must ensure a control strategy is in place for active substance batches used for their finished products.	17 April 2019 (last date of the Commission decisions related to the Article 31 referral adopted in 2019[5])
For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications: Limits for NDMA (96 ng/day) and NDEA (26.5 ng/day) should be implemented for the finished product. The limit should be calculated by dividing the respective limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC. The limit will usually need to be included in the finished product specification. Omission from the specification is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood. Skip testing is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 30% of the limits defined above and the root cause is identified and well-understood. In accordance with the recommendations adopted on N-nitrosamines impurities in human medicinal products (Article 5(3) procedure), where the co-presence of the above N-nitrosamines has been identified in the same finished product, it must be ensured that the cumulative risk of these N-nitrosamines does not exceed a lifetime cancer risk (lifelong exposure) of 1:100,000. An	30 June 2021

[5] Commission Implementing Decision C(2019)3157 (final) of 17.4.2019 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisation granted by Decision C(2016)1906(final) for "Amlodipine/Valsartan Mylan - amlodipine/valsartan", medicinal product for human use

alternative approach where the sum of these two N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified (NDEA) may also be used. The approach chosen for a particular case needs to be duly justified by the MAH. The MAH shall ensure that the control strategy for all N-nitrosamines is updated accordingly.	