

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



Expectations for the implementation of risk assessment and control strategies for nitroso impurities in substances covered by CEPs

Webinar 22 April 2021

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Timeline

June 2018:

N-nitrosodimethylamine (NDMA) discovered in valsartan

Root cause analysis highlighted presence of a nitrosating agent (sodium nitrite) and an amine (dimethylamine) after tetrazole ring formation



losartan, irbesartan, candesartan, olmesartan impacted



other amines lead to formation of additional nitrosamines NDEA, NDBA etc.

**Feb – April:
2019**

Art. 31 referral on sartans; CHMP opinion published and endorsed by EU commission

Jan 2020:

NDMA limited to 0.300 ppm and NDEA to 0.082 ppm for a transitional period (monographs revised);

'No nitrosamine' concept to follow in April 2021, i.e. NDMA, NDEA < 0.03 ppm

Timeline (2)

Following further reviews of CEPs for pioglitazone, ranitidine HCl, metformin HCl, CHMP opinion requested under Art. 5(3)

EU Article 5 (3) call for review to address nitrosamines

- MAH and API manufacturers to conduct appropriate investigations & risk assessments and inform authorities
- EDQM aligned with this approach for CEP substances

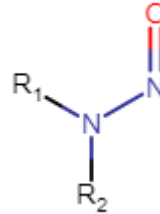
Timeline (3)

- July 2020:** CHMP opinion on nitrosamines in human medicinal products published;
- Aug 2020:** Publication of EMA Q&A document relating to the Article 5(3) opinion
- Nov 2020:** CHMP decision to align sartans with Article 5(3) opinion on other medicines
- April 2021:** Related sartan Ph. Eur. monographs revised again

Nitrosamines in (all) active substances

- *Stepwise approach for CEP holders:*
 - **STEP 1: RISK EVALUATION:**
 - conduct a risk assessment to identify any risk of nitrosamine formation
 - if there is a risk, inform EDQM with a testing plan and timelines
 - **STEP 2: CONFIRMATORY TESTING:**
 - provide test results to EDQM, and if needed a corrective actions plan with timelines
 - **STEP 3: UPDATE OF CEP APPLICATION**
 - implement additional controls or process changes
 - send revision application to EDQM as needed
 - completion by **26 September 2022 at the latest**
- *CEP holders should be supportive to MAHs and provide them with relevant information*

General information



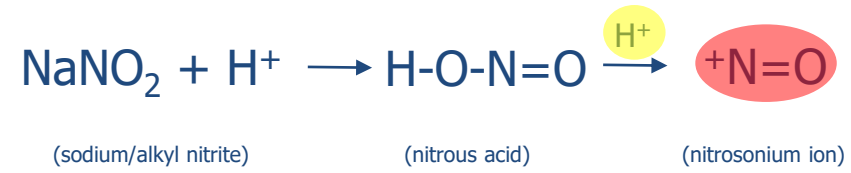
General structure of *N*-nitrosamines

ICH M7

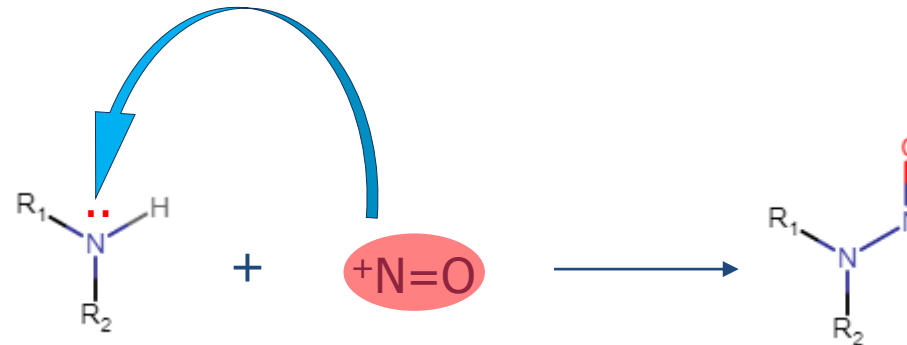
Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the “cohort of concern”, comprises aflatoxin-like-, *N*-nitroso-, and alkyl-azoxy compounds.

Formation of nitroso impurities

Stage 1



Stage 2



Amines

1° amines: generally considered as unlikely to directly result in nitrosamines as they are rapidly converted to diazo compounds

- cannot be entirely excluded as certain situations could favour their existence
- more likely, the risk is due to the presence of 2°/3° amines as impurities

2° amines: the most recognised source of nitrosamines as observed, not just in sartans, but in all active substances

- when not used directly, they are commonly found as impurities in other amines, so their presence is not always obvious; the most commonly observed are dimethylamine and diethylamine, leading to formation of NDMA and NDEA respectively

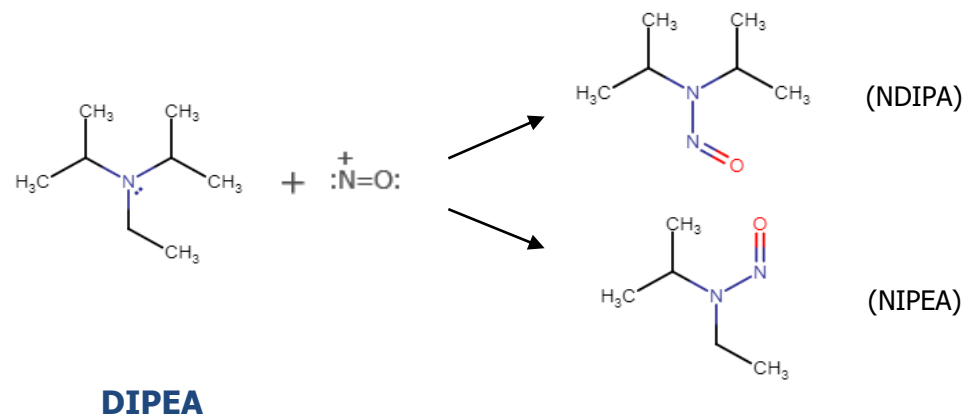
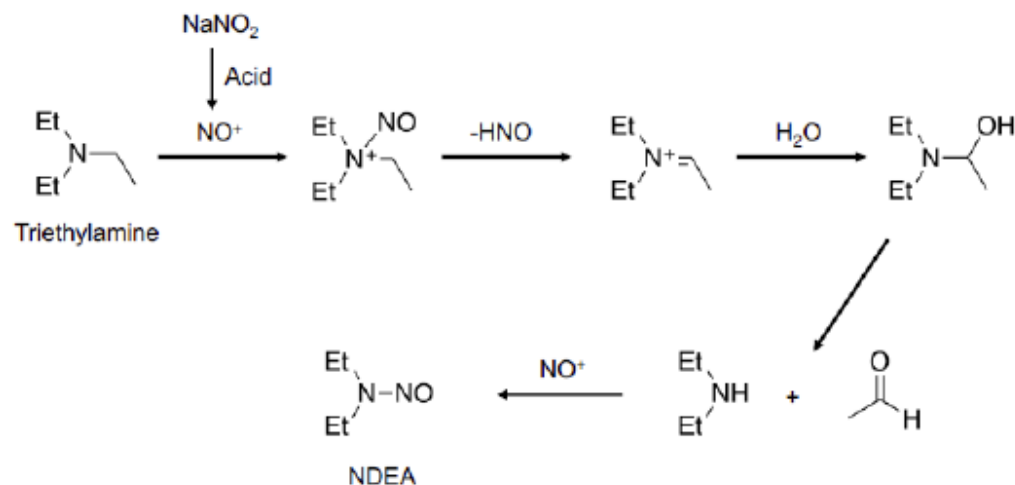
Amines

3° amines:

historically considered as not susceptible to nitrosation, but there are in fact 2 known pathways to nitroso formation

- direct nitrosation of the tertiary *N* atom followed by dealkylation
- the presence of 2°/3° amines as impurities

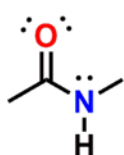
Fig. 4: Nitrosative cleavage of TEA to DEA followed by nitrosation to NDEA



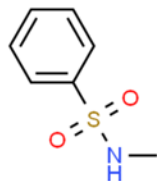
Amines

4° amines: often used as phase transfer catalysts, but have other uses also, e.g. tetrabutylammonium bromide (TBAB); most likely to form nitrosamines due to impurities e.g. dibutylamine may lead to NDBA

Other N-H groups:

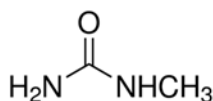


amide



sulfonamide

electron withdrawing groups, e.g. carbonyl compounds, have a tendency to deactivate the N-H group, which makes them less reactive to nitrosation leading either to no reaction or a slower reaction;



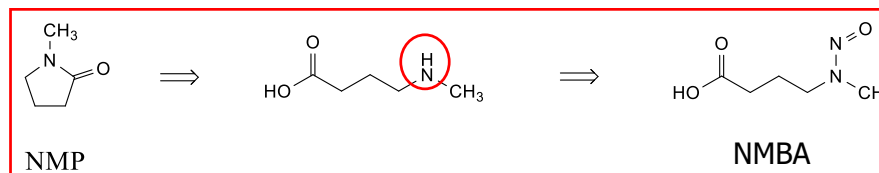
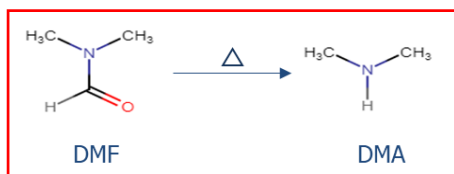
alkyl urea

N-alkylureas are known to more readily form nitroso derivatives possibly due to presence of electron inducing groups which may counteract the carbonyl function

High risk examples (not exclusive)

The presence of a nitrosating agent under acidic conditions when:

- Secondary/tertiary/quarternary amines are present in the same step;
- Raw materials that may undergo degradation to secondary/tertiary amines, e.g. DMF, Dimethylacetamide, *N*-methylpyrrolidone (NMP) are present in the same step;



- Recovery of solvents/materials may introduce an amino group to the same step*;
- Other N-H functional groups are present, e.g. alkyl amides, alkyl ureas etc., as though they are potentially less reactive, the reaction conditions may play an important role.

Medium risk examples (not exclusive)

The presence of a nitrosating agent under acidic conditions when:

- Secondary/tertiary/quarternary amines are used in a different part of the process and there is potential for carryover of either amine or nitrosating agent;
- Recovery of solvents/materials may introduce either an amine or nitrosating agent into a step before or after, thereby leading to potential carryover and interaction*

or

- Other N-H functional groups may be present, e.g. alkyl amides, ureas etc., as though they are potentially less reactive, the reaction conditions may play an important role.

* **NOTE:** Recovery procedures may introduce a source of nitrosating agent into the process though it is not specifically part of the synthetic process itself e.g. sodium nitrite used to quench excess sodium azide in recovery of solvent or raw materials.

Low risk examples

The absence of a source of nitrosating agent or amine would indicate a lower potential risk of nitroso formation, but the following scenarios could also be possibly viewed as lower risk (Note: 'lower' risk does not mean 'no' risk**):**

- Either N-H or nitrosating agent is present at a very early stage of the process (or starting material), so that potential carryover to possible nitroso-forming step is considered remote;
- Nitrites as impurities: important to be aware of cases where nitrite may be present as an impurity and may therefore pose a risk:
 - water (generally levels are very low);
 - sodium azide (again levels are generally very low);
 - other raw materials that may involve nitrite in their preparation, e.g. nitromethane

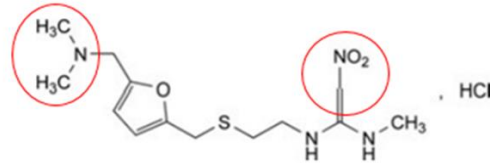
Other considerations

The following cases are less obvious pathways to nitrosation, but should be kept in mind nonetheless:

- degradation of the API (e.g. ranitidine exists as the hydrochloride salt and contains a nitro group and an amino function that forms NDMA at room temperature over time:

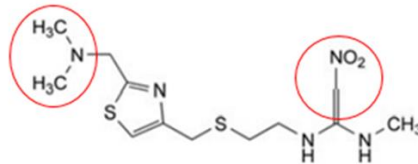
RANITIDINE HYDROCHLORIDE

Ranitidini hydrochloridum



NIZATIDINE

Nizatidinum



Other considerations (ctd)

- **production of nitrosating species:**

- catalytic reduction of nitrate (e.g. Pd) may lead to nitrite production;
- groups such as oximes (C=N-OH), hydroxylamine (NH₂OH) which may be susceptible to possible oxidation to nitrosating species;
- hydrazines (R-NH-NH₂) nitrosation may be possible, but spontaneous oxidation of certain hydrazines does occur e.g. 1-aminomethylpiperazine oxidises to methylnitrosopiperazine (*MeNP*);
- chloramine (NH₂-Cl), which may be used to disinfect water, is also known to react with diamino compounds to form nitroso impurities;
- GMP related issues due to cross-contamination, third party raw material recovery etc.

Assessment for CEP substances

Implementation of CHMP Opinion following Article 5(3) of Regulation (EC) No. 726/2004 for nitrosamine impurities in human medicines

including

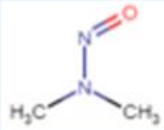
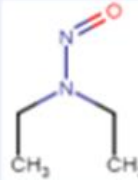
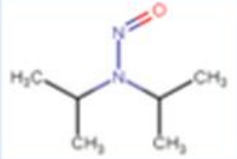
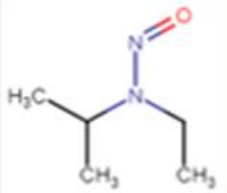
Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No. 726/2004 referral on nitrosamine impurities in human medicinal products

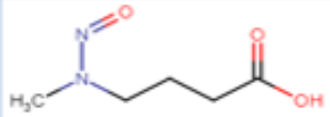
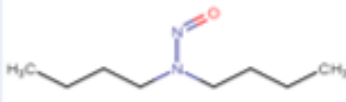
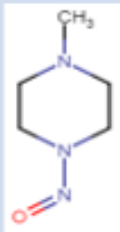
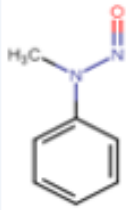
Scope

- Current guidance published with regard to nitrosamine impurities refers to human medicinal products only;
- Products exclusively reserved for veterinary use are out of scope;
- Anti-cancer drugs or active substances that are themselves mutagenic/clastogenic are also out of scope;
- The risk is primarily associated with chemically synthesised compounds, but certain fermentation products may be susceptible to nitrosamine contamination, so they should also be considered;

Limits

Acceptable intakes for specific nitrosamines as given in EMA Q&A document

Nitrosamine	Structure	AI (ng/day)
<i>N</i> -nitrosodimethylamine (NDMA)		96,0
<i>N</i> -nitrosodiethylamine (NDEA)		26,5
<i>N</i> -nitrosodiisopropylamine (DIPNA)		26,5
<i>N</i> -nitrosoisopropylethylamine (EIPNA)		26,5

Nitrosamine	Structure	AI (ng/day)
<i>N</i> -nitrosomethylaminobutyric acid (NMBA)		96,0
<i>N</i> -nitrosodibutylamine (NDBA)		26,5
1-methyl-4-nitrosopiperazine (MeNP)		26,5
<i>N</i> -nitrosomethylphenylamine (NMPA)		34,3

Limits ctd.

Two scenarios are foreseen for the treatment of other/new nitrosamines:

- if *N*-nitrosamines are identified with **sufficient** substance specific animal carcinogenicity data, TD_{50} should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7 (see CHMP Assessment report: 'Nitrosamine impurities in human medicinal products');
- if *N*-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7;
 - a class specific TTC for nitrosamines of 18 ng/day (derived from the Lhasa carcinogenic potency database) can be used as the default option;
 - an approach based on SAR considerations to derive an acceptable intake limit is acceptable, if appropriately justified e.g. NDBA limit based on structure similarity with NDEA.

Limits ctd.

The applicable limit should be calculated as follows:

$$\text{Limit (ppm)} = \frac{\text{AI (ng)}}{\text{MDD (mg)}}$$

- the Less Than Lifetime (LTL) concept is not considered suitable for highly toxic impurities (cohorts of concern) and should not be applied for nitroso impurities.
- for determining limits in the case of presence of more than 1 nitrosamine, 2 approaches are considered acceptable in order not to exceed the acceptable risk level of 1:100,000 as outlined in ICH M7:
 - the total daily intake of all identified *N*-nitrosamines not to exceed the AI of the most potent *N*-nitrosamine identified, or
 - total risk level calculated for all identified *N*-nitrosamines not to exceed 1 in 100,000.

Control strategy

The source of nitrosamine contamination must be identified/understood, so that impurity levels are expected to be consistent from batch to batch.

- test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient; as such, a control strategy in line with Options 1, 2 or 3 of ICH M7 may be applied in order to demonstrate that the nitroso impurity will not be present above the allowable limit derived from a suitable AI;
- a control strategy based on Option 4 of ICH M7 is not considered suitable in relation to nitroso impurities.
- omission of a specification in the API may be possible if the root cause of contamination is demonstrated to be well-understood, and if the amount of nitrosamine present is consistently below 10% of the acceptable limit based on the AI in the active substance, i.e. LOQ should be $\leq 10\%$ of the limit;

Control strategy ctd.

- if the related nitrosamine is formed in the last step of the process, a routine test is expected to be included regardless of whether or not values are found to be below 10% of the applicable limit;
- where the only risk of nitroso formation is from nitrite as an impurity, for example in sodium azide, or if carried through from an earlier step, a suitable control strategy based on carryover of nitrite may be acceptable if suitably justified and supported by spike purge studies (case by case);
- where nitrosamines are found above their respective limits, a thorough risk assessment should be carried out and corrective and preventive measures employed to ensure compliance with all current EU guidance.

Analytical methods

The analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities, commonly GC-MS and LC-MS. The following principles apply:

- the limit of quantification (LOQ) provides the minimum level at which an analyte can be quantified with acceptable accuracy and precision and should thus be used for impurity testing and decision-making;
- if quantitative testing is performed as a routine control, the LOQ should be \leq the acceptable limit based on the AI for the respective nitrosamine impurity;
- if quantitative testing is performed to justify omission of specification, the LOQ of the analytical method employed should be $\leq 10\%$ of the acceptable limit based on the AI.

Analytical methods ctd.

Exceptions may be considered for medicinal products used at high daily doses where limits may be below technical feasibility of the method, or in case more than 1 nitrosamine is anticipated or identified in a given medicinal product (such exceptions cannot be considered as part of the certification procedure, and must be approved by the competent authorities in the context of medicinal products).

For quantitative tests, attention should be paid to the validation data provided, particularly for accuracy/recovery, in order to be sure that related values are representative of the actual levels of nitrosamine in the substance. There are many examples of analytical methods on the EDQM website. The Ph. Eur. general chapter 2.5.42 may be used also.

The use of a limit test for routine control could possibly be acceptable in line with the validation requirements outlined in ICH Q2 when using a suitable reference solution.

Information resources

EDQM website: <https://www.edqm.eu/en/edqms-response-nitrosamine-contamination>

Further information

1. Lessons learned from presence of *N*-nitrosamine impurities in sartan medicines.
2. EMA assessment report 'Nitrosamine impurities in human medicinal products'.
3. EMA Q&A for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.

Thank you for your attention



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Nitrosamine control in the European Pharmacopoeia – special focus on monographs on sartans

Nitrosamines – CEP and Ph. Eur. approaches

Webinar 22 April 2021

Dr. Ulrich Rose

Head of Division A

European Pharmacopoeia Department

EDQM

Nitrosamine control and sartans

Content of the presentation

- Impurity control in Ph. Eur.
- Ph. Eur. General policy on DNA reactive impurities
- Control of Nitrosamines in Ph. Eur.
- Consequences for individual and general monographs
- Latest revision of sartan monographs

Control of impurities in Ph. Eur. (1)

Organic impurities

Inorganic impurities

Volatile impurities,
Water and residual
solvents

Special groups, e. g. DNA-
reactive imps, inorganics
subjected to Q3D

Control of impurities in Ph. Eur. (2)

- **Requirements concerning impurities are given in :**
 - Individual monographs
 - General monograph « *Substances for pharmaceutical use* », 2034
 - General chapters and texts, like 5.10: « *Control of impurities in substances for pharmaceutical use* »: helps to interpret the test for related substances in monographs on active substances, 5.20
« Elemental impurities » and others

Ph. Eur. General policy on DNA reactive impurities

➤ Ph. Eur. follows the principles of ICH M7

➡ Specifications to be set once an impurity has been shown to be mutagenic

➡ Structural alerts alone are considered insufficient to trigger follow-up measures

General policy on DNA reactive impurities

Individual monographs (1)

- What are the consequences for individual monographs?
- Include a specific test in the **test section** of a monograph or
- Include a statement in the **production section**

Production section: Statements in the production section constitute mandatory requirements for manufacturers. The statements or tests described cannot necessarily be verified by an independent analyst.

General policy on DNA reactive impurities

Individual monographs (2)

Two options:

- Include a specific test in the test section when a suitable method is available and acceptance criteria are known. Data on genotoxicity must be available.
- Include a statement in the production section when either no suitable, selective and sensitive test is known or the test would require too sophisticated equipment. In that case the MAH has to ensure the compliance of production with defined requirements.

General policy on DNA reactive impurities

General monograph 2034 (1)

« *Substances for pharmaceutical use* »

- A general monograph describes requirements that have to be fulfilled, not only for substances or preparations covered by an individual monograph but for all substances or preparations within the scope of the Definition section.
- General and individual monographs are complementary. If a provision of a general monograph does not apply to a particular product, this is expressly stated in the individual monograph.

General policy on DNA reactive impurities

General monograph 2034 (2)

« *Substances for pharmaceutical use* »

Related substances:

- Organic impurities controlled according to ICH Q3A
- “Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects.”**
- If the individual monograph does not provide suitable control for a new impurity, a suitable test for control must be developed and included in the specification for the substance

General policy on DNA reactive impurities

General monograph 2034 (3)

« *Substances for pharmaceutical use* »

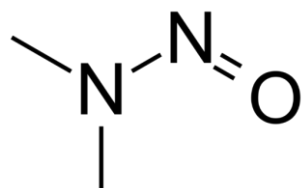
ICH M7:

« For DNA reactive impurities, the requirements of ICH Guideline M7 *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* must be complied with for active substances to be used in medicinal products for human use, in cases defined in the scope of the guideline. “

➤ *Revisions of general monographs 2034 and 2619 (pharmaceutical preparations) to align with recent regulatory decisions are ongoing*

Recap: Valsartan

- June 2018: information that Valsartan manufactured by Zhejiang Huahai Pharmaceutical (ZHP) was contaminated with NDMA (*N*-Nitrosodimethylamine)



NDMA is known as **possible carcinogen for humans** (well-known in the food area, may be present in water, smoked meat, BBQ...)

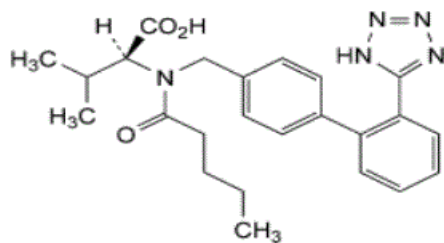
Nitrosamines are part of ICH M7 “cohort of concern”

- very low acceptable amounts, requiring sensitive analytical methods

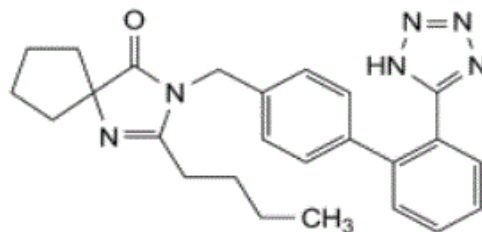
Classification of NDMA^[4]

American Conference of Governmental Industrial Hygienists (ACGIH)	A3: Animal carcinogen. “Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.”
International Agency for Research on Cancer (World Health Organization) (IARC)	2A: The agent (mixture) is probably carcinogenic to humans; there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.
National Toxicology Program (Health and Human Services Dept., Public Health Service, NIH/NIEHS) (NTP)	2: Reasonably anticipated to be carcinogens

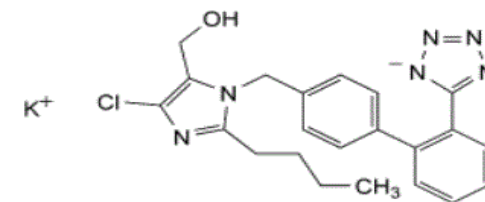
Sartans with a tetrazole ring structure in the Ph. Eur.



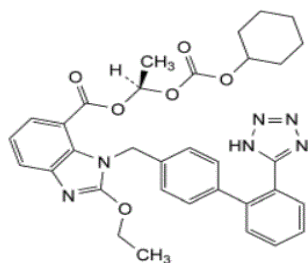
Valsartan



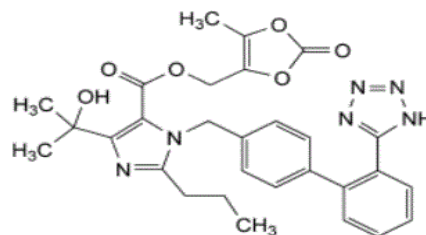
Irbesartan



Losartan potassium



Candesartan cilexetil



Olmesartan medoxomil

Implementation of the EU Art. 31 Referral outcome (sartans)

- Committee for Medicinal Products for Human Use (CHMP) opinion endorsed by EU Commission and published on 2 April 2019
- Transition period until 2nd of April 2021:
For all *N*-nitrosamines, the MAH must ensure a control strategy is in place in sartan API batches used for their drug products
→ Specifications must include the **interim limits for NDMA & NDEA. These were introduced in the test section of the Sartan monographs.**
E.g. Valsartan: NDMA 0.300 ppm, NDEA 0.082 ppm
- Latest CHMP opinion, published on 9. July 2020:

Recommendations regarding the the detection, management and prevention of presence of N-nitrosamines in **medicinal products for human use**. Press release on 13. 11. 2020: Alignment of these recommendation with Sartan medicinal products

Latest revision of Sartan monographs (1)

Production Section

As *N*-nitrosamines are classified as probable human carcinogens, their presence in valsartan should be avoided or limited as much as possible. For this reason, manufacturers of valsartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in valsartan. The general chapter 2.5.42. *N-Nitrosamines in active substances* is available to assist manufacturers.

Test Section

Interim limits for NDMA and NDEA deleted

Latest revision of Sartan monographs (2)

Implementation of these monographs:

- Revised monographs on 5 sartans were adopted on 5th of February 2021
- To avoid a gap between regulatory recommendations and mandatory pharmacopoeial monographs, the procedure of « rapid implementation » has been chosen:

5 revised Sartan monographs enter into force on 1st April 2021

The new general chapter **2.5.42, N-Nitrosamines in active substances** has been adopted in November 2020 and is already published on the EDQM website. 7 new nitrosamine reference standards are available.

Thank you for your attention



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-
- **Revision of CEPs referring to one of the “sartan” monographs following their rapid implementation**
 - <https://www.edqm.eu/en/news/revision-ceps-referring-one-sartan-monographs-following-their-rapid-implementation-0>

EU Article 5(3) opinion - Impact on sartans:

- CHMP decided to implement the Art 5(3) principles to sartans (published 13 November 2020)
- Impact on Sartans monographs: **tests removed, Production section reworted**

Implemented as Rapid Revision and implementation **1 April 2021** – texts published on the EDQM website

- Impact on CEPs for Sartans
 - **They are in compliance with the revised monographs**
 - **No pro-active revision of CEPs**, wait for submission of revisions (minor revision) by CEP holders

The revised monographs are an opportunity

- The change in the monographs, deletion from the tests section and revision of production section, is an opportunity to revisit the control strategy based on experience gained.
- The risk assessment can evolve based on increased process knowledge, better identification of sources of risk, and accumulated batch data.
- **What is really likely to be present and hence should be controlled?**
- Once the risk assessment has been revised the control strategy can then also be revised. The link between the two is essential. How the risk is controlled can change and a revised control strategy may lead to the deletion of controls from the CEP.
- ICH M7 **together** with EU Article 5(3) opinion and related Q & A to be taken into consideration in revision of a control strategy.

Revisions policy document (PA/PH/CEP (04) 2, 7R corr)

- 4.II.2 Control of the final substance
- 4.II.2.1 Change in the specification parameters and/or limits of the final substance
- g) Change of a limit for a mutagenic impurity in the final substance specification according to the principles and limits of the ICH M7 guideline.

A Minor revision

- **Documentation**
- 1. Comparative table of approved and proposed specifications.
- 3. Batch analysis data on two production batches of the final substance for all specification parameters.
- 5. Justification/risk-assessment from the Certificate holder as appropriate showing that the parameter can be deleted or widened according to the principles and limits of the ICH M7 guideline.

Change in control strategy

- A demonstration of the understanding of the process and the source of the risks is essential to allow assessors to accept revised control strategies.
- The expectations and guidance of the EU Article 5(3) opinion and related Q & A should be taken into consideration.
- When deciding on the limit, the PDE's for the nitrosamines are to be used in calculating an acceptable limit. Lower limits may also be applied and will be reported on CEP if included in specifications.
- The **need for a total limit** should be respected when more than one nitrosamine impurity is limited in the final substance.
- A justification should be provided if a total cannot be introduced (technical limitations of method, limits are at LOQ, limits very low.....)

Change in control strategy (2)

- Need to take into account definition of 'absence' in EU Referral and Q & A when showing the absence of a nitrosamine, LOQ is less than or equal to 10 % of the acceptable limit based on the AI to conclude in absence. If this cannot be done, absence cannot be concluded, and either a refined method needs to be used or a limit maintained/introduced for the nitrosamine.

Other changes related to nitrosamines

- Other changes made in the context of a revised control strategy need to be classified according to the Revisions policy document.
- **Changes to the manufacturing process to permit to lower levels are acceptable.**

Condition: it's a **replacement** and **no change to the qualitative** impurity profile of the final substance (e.g. no new solvents to be reported on CEP), **unless** the changes concern the control of mutagenic impurities whereby controls are transferred elsewhere and which then allow a deletion of a control in the final substance

- If this condition isn't met a separate sister file application should be submitted.
- This is for transparency, traceability and life cycle management reasons for **all** Certification procedure stakeholders.
- See announcement 21/7/2020
- Clarification on the acceptability of requests for revision of CEP applications (<https://www.edqm.eu/en/news/clarification-acceptability-requests-revision-cep-applications>)

Other changes related to nitrosamines (2)

- Examples would include:
changes to quenching procedures to destroy residual sodium azide,
changes in process flow where quenching would be offline,
change in reagent to avoid the formation of nitrosamines.
- These would be acceptable as a revision if the condition mentioned earlier are respected

THANK YOU FOR YOUR ATTENTION

QUESTION TIME