

# Risk evaluation and assessment for the presence of nitrosamine impurities in Alkaloid Losartan film coated tablets

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## Introduction

Nitrosamines are a class of chemical compounds, classified by the International Agency for Research on Cancer as group 2A carcinogens, i.e. potential genotoxic carcinogens, that were first described in the chemical literature over 100 years ago. Since in 2018 high levels of nitrosamines were detected in valsartan, they are once again subject of research (EMA/425645/2020, EMA/526934/2019, EMA/409815/2020 Rev.9).

Currently identified risk factors for N-nitrosamine impurities in medicinal products are grouped in the following categories: Risk factors related to the manufacture of the active substance; Risk factors also related to the finished product; and Risk factors related to Good Manufacturing Practice (GMP) aspects.

According to Art. 5(3) referral, Marketing Authorisation Holders (MAH) are requested to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesized Active pharmaceutical ingredients (APIs) or biological APIs (CMDh/412/2019, Rev.16). This evaluation should be performed in 3 sequential steps: (i) Risk evaluation, (ii) Risk confirmation test, (iii) Changes in Marketing authorisation (MA)

MAH must introduce the following specifications: limits for NDMA (96 ng/day) and NDEA (26.5 ng/day). 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.

## Materials and methods

PHA (Preliminary hazard analysis) tool was used for the risk evaluation to describe the risks identified through all Losartan film-coated tablets phases regarding the potential N-nitrosamine impurities formation.

The following risks were evaluated:

- Risks related to API Losartan Potassium synthetic route
- Risks related to the finished drug composition (excipients and primary packaging material)
- Risks related to the manufacturing process
- Risk of N-Nitrosamines formation during shelf life

## Results and discussion

### *Risks related to API Losartan Potassium synthetic route*

In the production of Alkaloid Losartan film coated tablets the API Losartan Potassium is used from two different manufacturers.

Both manufacturers have proven that their current synthetic route has low probability to form NDMA, NDEA or other related nitrosamines. This was confirmed with test result using validated GC-MS/MS method in which nitrosamines were not detected.

According to current guidelines, the following nitrosamines are controlled in the specification of the API manufacturers: NDMA, NDEA and NDBA with a limit of Not More Than (NMT) 0.03 ppm.

Based on the reviewed data the risk for formation of N-Nitrosamines from the API was identified as low

*Risks related to the finished drug composition (excipients and primary packaging material).*

Regarding the possible contamination coming from excipients and the process aids, none of the used excipients or process aids does not include nitro molecular species in their structure which are prerequisite for N-nitrosamine formation and all of the used excipients are of a well-established and long history of usage in pharmaceutical products. The evaluation was corroborated by the statements and evaluation provided by the excipients manufacturers.

The possible contamination coming from the primary packaging material was also evaluated. The primary packaging used for Losartan film-coated tablets is composed of Blister: PVC and aluminum foil. Although during sealing process temperatures of 180 °C or more are applied to the outside, time period of sealing is very short, normally less than one second. In addition, aluminum foil represents an absolute migration barrier and as soon as the lidding foil is sealed onto the blister material a migration of substances through the foil is not possible anymore and formation of nitrosamines is not expected during the packaging process.

Based on the reviewed data the risk for formation of N-Nitrosamines from the excipients or the primary packaging material was identified as low

*Risks related to the manufacturing process*

Since there was low risk of N-Nitrosamine formation and presence in regards of the excipients used and production process, where no nitrosating compound is introduced into the process, we considered that the risk for N-Nitrosamine formation in regards to the critical manufacturing process phases and conditions is also low. Cross-contamination is prevented by implemented organizational and technical measures and is regularly monitored. There are written procedures for cleaning of all product surfaces and cleaning validation is performed in order to confirm the effectiveness of the cleaning procedures. Cleaning agents used for the manufacturing equipment do not contain any substances which form nitrosamines. Therefore, the risk from cross-contamination was considered low.

*Risk of N-Nitrosamines formation during shelf life*

In regards to shelf life, since no risk of N-Nitrosamines was identified for: API, raw materials (excipients and primary packaging), process equipment,

critical process conditions and cross contamination, to the best of our knowledge we considered that there is low risk of N-nitrosamines formation during shelf life of the product.

Due to the conducted risk analysis where only low risk was identified per each evaluated element (API, excipients, manufacturing process, packaging and shelf-life) and overall low risk of N-nitrosamine presence or formation is assigned for Losartan film-coated tablets.

**Risk assessment (confirmation test) on the finished product**

Testing of Losartan film-coated tablets was performed using very selective and sensitive Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) method. Batches produced using API from both manufacturers were used for testing. The following criteria for the limit of NDMA and NDEA were established, based on ICH M7(R1) principles: NDMA  $\leq$  0.640 ppm; NDEA  $\leq$  0.177 ppm.

The results of the analyzed batches complied with the established specification. Results for NDMA and NDEA were "not detected". (Limit of quantification of the method was established as  $<$  0.009ppm)

**Conclusion**

Based on the conducted risk analysis where only low risk was identified per each evaluated element (API, excipients, manufacturing process, packaging and shelf-life) overall low risk of N-nitrosamine presence or formation is assigned for Losartan film-coated tablets.

**References**

- CMDh/412/2019, Rev.16 (CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines
- EMA/425645/2020 European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicine
- EMA/526934/2019 Lessons learnt from presence of N-nitrosamine impurities in sartan medicines
- EMA/409815/2020 Rev.9 (Questions and answers for marketing authorization 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