

## Risk evaluation for potential nitrosamine impurities for national authorised medicines for human use in the competence of the Paul-Ehrlich-Institut (Update February 2021)

Marketing authorisation holders of medicines containing chemically synthesized active pharmaceutical ingredients and biological active pharmaceutical ingredients are requested to submit a risk evaluation to the Paul-Ehrlich-Institut regarding the possible presence of nitrosamines for their medicinal products (step 1: risk evaluation). Medicinal products for which a risk is identified are to be tested and the corresponding test results to be submitted (step 2: risk assessment). In case changes to the marketing authorisation are necessary to prevent or limit the presence of nitrosamines to below the limits identified for the protection of public health, respective variations are to be submitted (step 3: changes to the marketing authorisation).

The call results from the procedure under Article 5 (3) of Regulation (EC) No 726/2004 on nitrosamines in medicinal products for human use.

### Nationally authorised medicinal products subject to Directive 2001/83/EC

Different submission timelines apply for medicinal products with chemically synthesized active pharmaceutical ingredients and biological active pharmaceutical ingredients. The deadlines are as follows:

Latest submission date:	MPs with chemically synthesized active pharmaceutical ingredients	MPs with biological active pharmaceutical ingredients
Step 1 (obligatory)	31/03/2021	01/07/2021
Step 2 and 3	26/09/2022	01/07/2023

For national authorised products the submission should be conducted in accordance with these guidance documents:

- 'CMDh practical guidance for marketing authorisation holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5 (3) Referral on Nitrosamines'
- 'CMDh questions and answers'

The website of the CMDh provides information with regard to procedural details as well as templates to be used.

#### Of note:

- It is possible to combine information for several medicines in one submission (one template), as long as the outcome or the risk evaluation is identical for the products concerned (see No. 1.2 of the CMDh 'practical guidance').
- According to CHMP Assessment Report<sup>1</sup> (EMA/369136/2020) dated 25/06/2020, there is a risk of presence of nitrosamines for biological medicinal products with certain risk factors. These are also listed under Q&A No. 2 in EMA/CMDh 'Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (EMA/409815/2020)'.

### Medicinal products approved according to § 4b AMG

Holders of approvals according to § 4b AMG are also requested to submit a risk assessment for their medicinal product approved according to § 4b AMG to submit a risk assessment with regard to a

<sup>1</sup> See Section 5 Recommendations, bullet point no. 2.

possible contamination with nitrosamines. The call applies mutatis mutandis to applicants whose application for initial approvals or subsequent approvals has not yet been decided and for whom no corresponding subsequent requirement has yet been formulated in the procedure.

Deadlines for products approved according to § 4b AMG:

Latest submission date:	ATMP nach § 4b AMG
Step 1 (obligatory)	01/10/2021
Step 2 and 3	01/10/2023

### Medicinal products approved under § 21a AMG and certain medicinal products authorised under § 21 AMG

The submission of a risk evaluation (step 1) is not required for marketing authorisation holders of blood components for transfusion and marketing authorisation/approval holders of human tissue preparations and stem cell preparations for haematopoietic reconstitution if no risk has been identified.

However, if a risk is identified, steps 2 and 3 must be carried out.

## Information and Templates of the CMDh and EMA

- Information of the Coordination Group (CMDh): [Information on nitrosamines for marketing authorisation holders](#)
- Information of the EMA: [Nitrosamine impurities](#)

## Submission and contact

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## Background

In June 2018 a contamination of valsartan with nitrosamine N-nitrosodimethylamine (NDMA) was detected.

Since then nitrosamine impurities have also been found to be present in batches of other medicines with chemically synthesised active pharmaceutical ingredients. It is now known that these impurities can form during production under certain conditions and when certain solvents, reagents and other raw material are used.

On the basis of animal experiments nitrosamines are classified as potentially carcinogenic in humans. They may be present in certain foodstuff and potable water. It is not expected that nitrosamines cause harm when ingested in marginal amounts.

Despite the low risk that nitrosamine impurities are present, a [scientific evaluation on nitrosamine impurities](#) by the Committee for Medicinal Products for Human Use (CHMP) was initiated in September 2019 in accordance with Article 5(3) of Regulation (EC) No 726/2004.

Resulting from that and to begin with, in September 2019 a risk evaluation and, if relevant, testing was requested only for medicinal products with chemically synthesised active pharmaceutical ingredients. According to the CHMP Assessment Report (EMA/341963/2020) dated 25/06/2020 also a risk of nitrosamine contamination for biologics with certain risk factors was identified and further measures were adopted. As per July 2020, marketing authorisation holders of medicinal products with biological active pharmaceutical ingredients are also requested to conduct a risk evaluation. This also applies to centrally authorised ATMPs.

To ensure patient protection, a corresponding risk assessment procedure is now being carried out for ATMPs that are approved nationally according to § 4b AMG.