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EMA advises companies on steps to take to avoid nitrosamines in human medicines

EMA's human medicines committee (CHMP) is requesting as a matter of precaution that marketing authorisation holders for human medicines containing chemically synthesised active substances review their medicines for the possible presence of nitrosamines and test all products at risk. If nitrosamines are detected in any of their medicines, marketing authorisation holders must inform authorities promptly so that appropriate regulatory actions can be taken.

A [notice](#) to this effect is being sent out to marketing authorisation holders with information on the actions they should take. A [questions-and-answers](#) document is also available on EMA's website.

Marketing authorisation holders are responsible for ensuring that every batch of their finished product is of satisfactory quality, including the active substances and other ingredients used to make them. They should take into account the published guidance along with knowledge of the manufacturing processes for their products and all other relevant scientific evidence.

Steps companies should take

- Evaluate possibility of nitrosamines being present in every concerned medicine within 6 months
- Prioritise evaluations, starting with medicines more likely to be at risk of containing nitrosamines
- Take into account findings from CHMP's review of sartans
- Notify authorities of outcome of risk evaluations
- Test products at risk of containing any nitrosamines
- Immediately report detection of nitrosamines to authorities
- Apply for necessary changes to marketing authorisations to address nitrosamine risk
- Complete all steps within 3 years, prioritising high risk products

Nitrosamines are classified as probable human carcinogens, which means that long-term exposure above certain levels may increase the risk of cancer. They are present in some foods and drinking water supplies and where they have been found in medicines the risk of developing cancer has been [low](#).



Although nitrosamines are not expected to form during the manufacture of the vast majority of medicines containing chemically synthesised active substances, it is important that all companies who have not already done so take appropriate precautionary measures, if necessary, in line with recommendations from the recently concluded [review of sartans](#).

EMA will continue working closely with national authorities, [EDQM](#) and international partners to ensure that companies are taking appropriate measures to prevent nitrosamine impurities from being present in their products.

In the meantime, the CHMP will continue evaluating available scientific knowledge on the presence of nitrosamines in medicines and advise regulatory authorities on actions to take if companies find nitrosamines in their medicines.

Patients and healthcare professionals are advised to continue using their medicines as normal taking into account recommendations in the product information.

Notes

- The guidance from the CHMP follows a request by EMA's Executive Director according to [Article 5\(3\) of Regulation \(EC\) No 726/2004](#), which allows the CHMP to draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use.
- The guidance draws on work carried out in conjunction with the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein and Norway.
- The second phase of the Article 5(3) procedure is still ongoing. In this second phase, the Committee will continue evaluating all available scientific knowledge on nitrosamine impurities and will consider, among other things, whether to broaden the scope of the review to include medicines other than those containing chemically synthesised active substances.
- For centrally authorised medicines, further information will be posted on EMA's website. Information on non-centrally authorised medicines will be posted on the [CMDh website](#).