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Questions & Answers on implementation: 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)

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Implications of the new Commission Decision

In November 2020 the CHMP adopted an Opinion concluding that the outcome of the Article 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471) should be aligned with the outcome of the Article 5(3) assessment on nitrosamines (EMEA/H/A-5(3)/1490). The main change concerns the limits for N-nitrosamines, which previously applied to the active ingredients and will now apply instead to the finished products.

In line with previous opinion, companies should have appropriate control strategies to prevent or limit the presence of nitrosamine impurities as much as possible and, where necessary, improve their manufacturing processes. Companies should also evaluate the risk of N-nitrosamines being present in their medicines and carry out appropriate tests when a risk has been identified.

This leads to the following revised conditions to the concerned marketing authorisations (MA) of tetrazole sartans:

	Conditions to the MA of tetrazole sartans	**Due date**
A	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
B	(New) 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
C	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)

D	(New) 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 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.	30 June 2021

Further to this CHMP opinion, the European Commission (EC) has adopted new decisions amending the previously published Commission Decisions with the above amended Conditions.

As a consequence, within 30 days after publication of the Commission Decision MAHs should implement the updated conditions in their marketing authorisation either through taking the opportunity of an on-going variation application affecting the Product Information, or through the submission of a type IA_{IN} C.I.1.a variation application.

The MAH should ensure that their marketing authorisation is brought up to date with all the conditions as reflected in the recent EC decision.

1. The new Commission Decision only includes limits for NDMA and NDEA. Which limits apply for other N-nitrosamine impurities?

Sartans products containing a tetrazole ring are covered also by the call for review for chemically manufactured medicinal products. Should as part of the risk assessment (reflected as conditions A and B) other or further nitrosamines be detected in the API and/or finished product, this should be reflected in the dossier as appropriate. Reference is also made to Question 10 of the 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 N-nitrosamine impurities in human medicinal products (EMA/409815/2020).

2. Should a limit for N-nitrosamine impurities always be included in the MA dossier?

A limit for NDMA and NDEA will usually need to be included in the MA as specification for the finished product to be taken into account for the batch release and the shelf life.

If duly justified the control point for nitrosamines can be selected to give assurance of presence of the impurity below the limit in the finished product.

Omission from the inclusion of specification is only justified if it can be shown that the level of the respective N-nitrosamine is consistently ≤ 10% of the limit defined in condition D, the root cause is identified and well-understood and the LoQ of the analytical method employed is ≤ 10% of the limits.

Skip testing is only justified if it can be shown that the level of the respective N-nitrosamine is consistently ≤ 30% of the limits defined in condition D, the root cause is identified and well-understood and the LoQ of the analytical procedure employed is ≤ 30% of the limits.

Reference is made to Questions 9 and 15 of the 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 N-nitrosamine impurities in human medicinal products (EMA/409815/2020).

3. Which variations are necessary to lift the conditions on the MA?

Condition A

For lifting the condition on the risk assessment (RA) for the active substance there are 3 possibilities[1]:

1. When the risk assessment is done and resulted in no changes to the manufacturing process being necessary, the MAH has to submit this outcome of the risk assessment in the appropriate variation application in order to lift the condition via a type IAIN C.I.11.a variation (if not already done).
2. When the risk assessment resulted in necessary changes of the control strategy and, if necessary, manufacturing process the appropriate variation(s) applications(s) should be submitted. As an example, for drug substances based on full data presented in Module 3.2.S, a non-exhaustive list of variations required to ensure a control strategy for confirmed presence of N-nitrosamines may include a type IB variation B.I.a.4.f to change in-process tests, a type IB variation B.I.b.1h to change specifications parameters of a starting material/intermediate/reagent. For drug substances based on a CEP, the updated CEP should be filed by the MAH via type IA or IB (B.III.1a) variation application to lift the conditions to the MA.
3. When the risk assessment results in the need for change to the manufacturing process, a type II variation application (B.I.a.2.b) has to be submitted for full data in 3.2.S or a variation B.III.1 (type IA or IB) in case of updated CEPs to the lift the condition to the MA.

[1] The e-Application form (eAF)will be updated to select the option that the variation is linked to nitrosamine related aspects

Condition B

For lifting the condition on the risk assessment for the finished product, the MAH should submit a step 2 response in the general "call for review" mentioned above and justify the removal of the Condition from Annex II as part of an appropriate variation[2]. In addition, if a risk has been confirmed in step 2 appropriate variation application(s) should be submitted as relevant to implement changes to the manufacturing process.

Condition C

For lifting the condition on the control strategy for active substance, a declaration of the MAH that a control strategy is in place has to be submitted via a type IAIN C.I.11.a variation (if not already done).

Condition D

For lifting the condition on the change of the finished product specification, the MAH should submit a type IB B.II.d.1.g variation application (addition or replacement of a specification parameter as a result of a safety or quality issue) and update the MA accordingly.

If the MAH wants to apply for omission from the specification, then supporting data should be submitted via a type IB C.I.11.z variation (see also Question 2 above).

MAHs are encouraged to submit these variation applications via grouping/worksharing procedures when possible.

In addition, the MAHs should clearly indicate in the section scope and background of the application form that the variation application is submitted in order to lift the condition(s) on the MA and state to which condition (A,B,C,D) it relates.

[2] If the risk assessment resulted in in no necessary changes, a variation should be submitted to lift the condition. If the outcome of the risk assessment requires assessment, a type IB variation C.I.11.z is recommended.
If changes are necessary, the condition can be lifted with the approval of the relevant variation.