CMDh Questions & Answers on implementation of outcome of Art. 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group

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4. What are the implications of the new Commission Decision?

In October 2020 the CHMP concluded 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 but will now apply instead to the finished products. In line with previous recommendations, 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.

This leads to the following revised conditions to the MA of tetrazole sartans:

<table>
<thead>
<tr>
<th>Conditions to the MA of tetrazole sartans</th>
<th>Due date</th>
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<tbody>
<tr>
<td>A</td>
<td>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</td>
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<tr>
<td>B</td>
<td>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.</td>
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<td>C</td>
<td>For all N-nitrosamines, the MAH must ensure a control strategy is in place for active substance batches used for their finished products.</td>
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<td>D</td>
<td>For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications:</td>
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<td>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.</td>
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<td>The limit will usually need to be included in the finished product specification.</td>
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<td>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.</td>
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<tr>
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<td>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.</td>
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<td>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.</td>
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<td>The MAH shall ensure that the control strategy for all N-nitrosamines is updated accordingly.</td>
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MAHs have to submit a type IAIN C.I.11.a variation to include the new conditions in the marketing authorisations within 10 days after publication of the Commission Decision.

The MAH should review the new conditions against any variation previously submitted in fulfilment of the previous conditions and submit further variations as necessary or confirm fulfilment of the new conditions.

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

Reference is 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).

6. **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 finished product specification (to cover release and shelf life specifications).

If duly justified the control point for nitrosamines can be selected in such a way that it will give assurance of presence of the impurity below the limit in the finished product.

Omission from the specification is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently $\leq 10\%$ of the limit defined in condition D, the root cause is identified and well-understood and the LoQ of the analytical method employed is $\leq 10\%$ of the limits.

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

Reference is made to Questions 9 and 15 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).

7. **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. When the risk assessment is done and resulted in no necessary changes to the manufacturing process the MAH has to submit this outcome of the risk assessment in a variation C.I.11.a in order to lift the condition (if not already done so, as this condition remained from the initial Referral Commission Decision in 2019).

2. When the risk assessment resulted in necessary changes of the control strategy and if necessary manufacturing process suitable variation(s) should be submitted. As an example, for drug substances based on an updated ASMF or full data presented in Module 3.2.5, 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 or if the change is included in the restricted part of the ASMF, a type IB variation B.I.a.2.e could be submitted. 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. With approval of the relevant variation(s) the condition can be lifted.

3. When the risk assessment resulted in a necessary change of the manufacturing process a type II variation B.I.a.2.b has to be submitted for ASMF and full data in 3.2.S or a variation B.III.1 (type IA or IB) in case of updated CEPs. With approval of this variation the condition A can be lifted.

**Condition B**

For lifting the condition on the risk assessment (RA) for the finished product the MAH should submit a step 2 response in the general "call for review". Reference is made to the CMDh practical guidance document for MAHs of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines (CMDh/412/2019).

In addition, appropriate variation application(s) should be submitted to implement changes to the manufacturing process, if a risk has been confirmed in step 2.

**Condition C**

For lifting the condition on the control strategy, a declaration of the MAH, that this is in place, has to be submitted via a type IAIN C.I.11.a variation (if not already done so as this condition remained from the initial Referral Commission Decision in 2019).

**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 (addition or replacement of a specification parameter as a result of a safety or quality issue).

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 6 above).

MAHs are encouraged to submit these variation applications via worksharing procedures if possible.

In addition MAHs should clearly indicate in the section scope and background in 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.