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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1. In the CMDh press release of March 2019 it was published that the necessary CEP updates can be submitted as type IA variations (B.III.1). However, as condition No. 2 to this requires variation specifications for relevant impurities to remain unchanged (unless tightened); at least for the implementation of the transitional limits the condition 2 for an updated CEP cannot be fulfilled until the updated monographs come into force. What to do in this respect?

In case there is a change in the additional to Ph. Eur. Monograph specifications for impurities in the CEP, the variation B.III.1 has to be submitted as a type IB variation in which case the amended specification and the analytical method used is then automatically included.

Question deleted in December 2020.

2. Some CEPs for the sartans do not yet contain a specification on nitrosamine testing as the risk assessment provided by the API manufacturers has not resulted in any risk on N-nitrosamine contamination. Is a variation application still needed and if so which type of variation?

A variation is always required to implement an update to the CEP even if it is not accompanied by a specification change. In case the CEP has not been updated by EDQM, there is no need to submit a CEP related variation (B.III.1). However, in both cases, the required updates to the registered API specifications from the API manufacturer and the finished product manufacturer have to be immediately implemented for all sartans independent from the outcome of the risk assessment. Therefore, the amended API specification has to be introduced in the dossier by a type IB variation (B.I.b.1.h). Moreover, it is underlined that in any case, if the CEP does not contain a specification on nitrosamine testing, such testing is expected to be performed by API manufacturer and the finished product manufacturer to be compliant with the conditions to the Marketing Authorisation in Annex IV of the Commission Decision. It should be noted that the updated Ph. Eur. monographs on sartans will be in force in January 2020 and all CEPs will be brought in compliance with these revised standards and carry limits for nitrosamines from that date.

Question deleted in December 2020.

3. A variation application is submitted to add a new API manufacturer for a sartan (included in the scope of the referral) using an ASMF or a CEP. How will these procedures be handled?

For those using an ASMF, a risk assessment concerning nitrosamine contamination has to be performed and submitted at the latest during the clock stop. The API specification of API and FP manufacturer has to be amended according to the limits mentioned in the Commission Decision. Upon approval of the variation the transitional limits have to be introduced. The final limits should be implemented within 2 years after publication of the Commission Decision by a separate variation.
procedure. For those using CEPs the advice as given in the CMDh press release from March 2019 should be followed, see also Q&A 1 and 2 above.

2. The Commission Decision only includes limits for NDMA and NDEA. In the meantime, limits have been agreed at EU level for NMBA, DIPNA and EIPNA. How is this dealt with? Do MSs impose these limits during new marketing authorisation applications and/or variation applications?

In case of potential nitrosamine formation, the RMS should ask for a risk assessment by the applicant. If the company’s risk assessment shows that there is a risk for formation of other nitroamine impurities, limits should be included in the drug substance specification of the API and FP manufacturers. For NMBA, DIPNA and EIPNA transitional limits have already been agreed at a European level and could be used as reference (see table below). The final limit (i.e. 0.03 ppm) should be implemented within 2 years after publication of the Commission Decision by a separate variation procedure. If another nitroamine impurity is identified, this should be highlighted to the RMS, as the limit to be implemented should then be discussed at a European level. It is strongly advised to also consider the implementation of limits for other nitroamines for already approved products, should the risk assessment conclude that formation of these impurities is possible.

Question deleted in December 2020.

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>
</tr>
</thead>
<tbody>
<tr>
<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 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</td>
<td>17 April 2021</td>
</tr>
</tbody>
</table>
**B**  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)

**A**  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.

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<td></td>
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<td>26.5</td>
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<td>96.0</td>
</tr>
<tr>
<td>Candesartan</td>
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<td>26.5</td>
<td>0.820</td>
<td>96.0</td>
</tr>
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</table>

3. Is skip testing acceptable for NDMA and NDEA?

Routine testing for NDMA and NDEA should be implemented. Skip testing is not considered acceptable at this time as sufficient evidence that a state of control exists to limit nitrosamine contamination within sartan drug substances is not yet available. CHMP considered that skip testing would not be appropriate given the potential risks of contamination (including cross-contamination), the batch-to-batch variability observed so far, and considering the very low acceptable levels of such impurities (i.e., the capability of analytical methods to determine that only a negligible amount of these impurities is present). Given the various potential sources of N-nitrosamines impurities, introducing a limit in the API specification was considered by the CHMP as the most appropriate control measure to prevent the risk of releasing batches contaminated.

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 ≤ 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 levels of the respective N-nitrosamines are 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 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 marketing authorisations? MA?**

**Condition 1A**

For lifting the condition No 1 on the control strategy, a declaration of the MAH, that this is in place, has to be submitted in a variation C.I.11.a.

**Condition 2**

For lifting the condition No 2 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 single variation also the lifting of the condition No 1 on the control strategy can be included, 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.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 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 No 3A can be lifted.

**Condition 3B**

For lifting the condition No 3 on the change of the API specification with the interim limits, one of the following variations should be submitted:

- For drug substances based on an updated ASMF or full data presented in Module 3.2.S a type IB variation (B.I.b.1.h) has to be submitted, unless the updated specifications are included in a type II variation (B.I.zr risk assessment (RA) for the update of ASMF/ Module 3.2.S
- If the changes are made following an update of the Ph Eur specification (i.e. in order to comply with the updated relevant Ph. Eur. Monograph), they may be submitted as variation (B.III.2.b). This variation has to be submitted as type IB variation, if condition 4 “Additional validation of a new or changed pharmacopeial method is not required” is not fulfilled (in situations where the Ph.Eur. Monograph does not include an analytical method for the determination of nitrosamine).

For drug substances based on a CEP, the updated CEP should be filed by the MAH via type IA (B.III.1a), if all conditions are fulfilled. In particular, it should be confirmed that the CEP analytical method is used for API testing by the drug finished product manufacturer as well. Otherwise, if the MAH used a different analytical method for API testing an additional type IB variation (B.I.b.2.e) variation is required. In case the drug product manufacturer wishes to register different specifications for the control of nitrosamines, an additional type IB variation (B.I.b.1.h) may still be needed 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).

With approval of the relevant variation(s) the condition No 3 can be lifted.

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 4C**

For lifting the condition No 4 on the control strategy, a declaration of the MAH, that this is in place, has to be submitted via a type IA variation 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 API specifications within finished product specification the final limits after MAH should submit a maximum of 2 years after the Commission Decision, a further type IB.B.II.d.1.g variation B.I.b.1.h(addition or B.III.1 in case replacement of a specification parameter as a result of updated CEPs has a safety or quality issue).
If the MAH wants to apply for a change in omission from the API specification with the final limits as for condition No 3. With approval of the relevant variation(s) the condition No 4 can be lifted, then supporting data should be submitted via a type IB C.I.11.z variation (see also Question 6 above).

If the MAH directly amends the API specification to the final limits, conditions Nos 3 and 4 might be lifted simultaneously with approval of these variations.

A variation to include the conditions and to lift conditions Nos 1 and 2 may be grouped with a variation to lift conditions Nos 3 or 4. They cannot be submitted as a single variation. 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.