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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?

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?

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?

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:

	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	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	26 September 2022

	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.	
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	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

The revised conditions from the updated article 31 referral for sartan medicines supersede the previous conditions applied. As the previous conditions no longer apply the MAH should replace any outstanding conditions listed on the authorisation with the revised conditions from the article 31 referral via a type IAIN C.I.11.a variation within 10 days after publication of the Commission Decision. All conditions stated in the revised referral should be applied to the licence at the same time and the MAH should

refer to Q7 for the requirements and further submissions necessary to lift the revised conditions from the authorisation.

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 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.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 A can be lifted.

Condition B

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).

NB: For sartans containing a tetrazole group a step 2 response is always needed; it is not possible to report a step 1 'no risk' outcome.

For lifting the condition on the risk assessment (RA) for the finished product there are two possibilities:

1. If no nitrosamine has been detected in step 2 or levels are below 10% AI (Scenario C*) the MAH has to submit the outcome of the risk assessment in a type IA C.I.11.a variation in order to lift the condition B.
2. If nitrosamine has been detected in step 2 above 10% AI (Scenario A and B*), appropriate variation application(s) should be submitted to implement changes to the manufacturing process and following the requirements of the Art. 5(3) Q&As. When the respective variation is submitted to the NCAs and approved, the underlying condition will be lifted automatically. However, companies have to clearly address in the section scope and background in the application form that this variation is submitted in order to lift the respective condition in the MA.

* EMA/425645/2020 European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines

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). If this variation is refused, the MAH should submit a type IB B.II.d.1.g variation at their earliest opportunity, but not later than 31 December 2021.

General comments

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.

A variation to include the new conditions may be grouped with one or more variations to lift conditions, but they cannot be submitted as a single variation.

8. How to deal with products that are currently not marketed?

The conditions apply to all products under the scope of the referral, irrespective of the marketing status of the product. However, it is recognized that a step 2 response (condition B) and a variation to include limits for NDMA and NDEA in the finished product specification (condition D) may not be possible for medicines that are not marketed since there may be no finished product batches available for confirmatory testing. In these cases, it would be acceptable to submit a written confirmation that the outcome of step 2 confirmatory testing and necessary variation will be submitted before the product is launched. This commitment should be submitted via a type IA C.I.11.a variation. It has to be clearly outlined in the section scope and background in the application form that the variation application is submitted in order to delay implementation of the condition(s) on the MA.