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.

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 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.

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.

4. 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 nitrosamine
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 nitrosamine 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 nitrosamines for already approved products, should the risk assessment conclude that formation of these impurities is possible.

<table>
<thead>
<tr>
<th>API</th>
<th>Max. daily dose (mg)</th>
<th>DIPNA, EIPNA AI(ng/day)</th>
<th>DIPNA, EIPNA Corresponding concentration level (ppm in API)</th>
<th>NMBA AI(ng/day)</th>
<th>NMBA Corresponding concentration level (ppm in API)</th>
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</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>320</td>
<td>26.5</td>
<td>0.082</td>
<td>96.0</td>
<td>0.300</td>
</tr>
<tr>
<td>Losartan</td>
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<td>26.5</td>
<td>0.177</td>
<td>96.0</td>
<td>0.640</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>40</td>
<td>26.5</td>
<td>0.663</td>
<td>96.0</td>
<td>2.400</td>
</tr>
<tr>
<td>Irbesartan</td>
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<td>26.5</td>
<td>0.088</td>
<td>96.0</td>
<td>0.320</td>
</tr>
<tr>
<td>Candesartan</td>
<td>32</td>
<td>26.5</td>
<td>0.820</td>
<td>96.0</td>
<td>3.000</td>
</tr>
</tbody>
</table>

**5. 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.

**6. Which variations are necessary to lift the conditions on the marketing authorisations?**

**Condition 1**

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 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. (In this single variation also the lifting of the condition No 1 on the control strategy can be included.)
2. When the risk assessment resulted in necessary changes of the control strategy 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 2 can be lifted.

**Condition 3**

For lifting the condition No 3 on the change of the API specification with the interim limits, a type IB variation (B.I.b.1h) has to be submitted for a change in one of the API specification with the transitional limits for following variations should be submitted:

- **For** drug substances based on an updated ASMF or full data presented in Module 3.2.S. For drug substances based on a CEP, CEP holders should file a variation application at EDQM. The updated CEP should be filed by the MAH via type IA or IB (B.III.1a) variation application and, if needed, the amended specifications have to be introduced into the dossier by a type IB variation (B.I.b.1h). However, if has to be submitted, unless the updated specifications are included in a type II variation (B.I.z) for the update of ASMF/Module 3.2.S.

- **If** the changes are made following an update to 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 pharmacopoeial 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 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) 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.

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

**Condition 4**

For lifting the condition No 4 on the change of the API specifications with the final limits after a maximum of 2 years after the Commission Decision, a further variation B.I.b.1.h or B.III.1 in case of updated CEPs has to be submitted for a change in 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.

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.