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

Table of contents

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 can not be fulfilled until the updated monographs come into force. What to do in this respect? ................................................................. 2

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? ..... 2

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? ................................................................................... 2

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. ................................................................................................................................. 2

How is this dealt with? Do MSs impose these limits during new marketing authorisation applications and/or variation applications? ........................................ 2

5. Is skip testing acceptable for NDMA and NDEA? ........................................... 3
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 can not 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>
</tr>
</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>
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<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.