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CHMP List of questions

To be addressed by the API manufacturers for valsartan-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1471

Active substance: valsartan

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1. Background

Valsartan is an angiotensin-II-receptor antagonist authorised in the EU as a single agent or in combination with other active substances and indicated for the treatment of hypertension, recent heart attack and heart failure, both in nationally and centrally authorised medicinal products.

The EU authorities were notified that an Active Pharmaceutical Ingredient (API) manufacturer (Zhejiang Huahai Pharmaceutical, China) has detected the presence of a previously undetected impurity, N-nitrosodimethylamine (NDMA, also known as dimethylnitrosamine) in the valsartan API manufactured at its site in Chuannan. Zhejiang Huahai is one of the API manufacturers that are supplying valsartan for medicinal products authorised in the EU.

NDMA is a genotoxic and carcinogen agent in animals and it is classified as a probable human carcinogen by IARC (International Agency for Research on Cancer, WHO).

An initial investigation report on the root cause of the presence of NDMA by the manufacturer indicates that NDMA formed at a specific step in the valsartan API manufacturing process, and the level of NDMA present may depend on the reaction conditions used.

According to tests of a small random selection of API batches performed by this manufacturer, the levels of NDMA detected range between 3.4 ppm to 120 ppm, with an average of 66.5 ppm. According to the principles of ICH-M7, these levels raise concerns, considering that NDMA belongs to the group of N-nitroso compunds.

The EC requested on 5 July 2018 the initiation of a Referral under Article 31 of Directive 2001/83/EC.

2. Questions

The valsartan API manufacturers are requested to address the following questions:

To all API manufacturers with confirmed presence of NDMA in the API:

Please provide summaries and any updates since the last response to EMA on the below points:

1. The manufacturer is requested to provide information on the NDMA content in API batches manufactured for medicinal products authorised in the EU/EEA that are at risk of containing NMDA (e.g. following manufacturing changes). In addition, information on the progress of the testing plan and any interim results should be provided.

2. Please comment on any variability of the contamination in batches tested, e.g. in view of any process parameters that may specifically impact on the formation of NDMA or potential difference in equipment when different workshops are used.

3. Please provide details on
   a) the analytical quantification method for detecting NDMA in the API valsartan, the limit of detection, limit of quantification and comment on the validation status of this method.

   b) any proposed corrective and preventive actions to ensure that the manufacturing process does not generate NDMA or yields NDMA levels within the acceptably daily intake. Please comment on potential foreseen changes to manufacturing process, in-process controls, specifications and related analytical methods for the API and their validation.

To all other API manufacturers:

1. NDMA appears to be generated during the formation of the tetrazole ring by reaction of dimethylamine (which may be present as an impurity or degradant in the solvent dimethylformamide (DMF)) and sodium nitrite under acidic conditions (where nitrous acid is formed). It can also not be excluded that other *N*-nitrosamines could be generated with other solvents or under other specific reaction conditions where other amines are present.
   Please provide information if you currently are using (or have in the past used) any step in the valsartan manufacturing process that may potentially lead to the generation of NDMA or any other possible *N*-nitroso impurity.

2. If the answer to Q1 is yes, you are requested to provide details on:
   a) when was this process introduced for the manufacture of valsartan (or for how long it has been used, if in the past);

   b) what NDMA levels are in batches of active substance. Please, provide the full details of the analytical methods used to identify and quantify NDMA, including the method validation;

   c) if levels have not been determined yet, what is your plan to do so in terms of test sampling strategy, development of relevant analytical method and validation;

   d) any mitigation steps in the current (or past) manufacturing process to reduce, eliminate, or avoid formation of NDMA during the process or from the finished API;

   e) any proposed corrective and preventive actions to ensure that the manufacturing process does not generate NDMA or yields NDMA levels within the acceptably daily intake. Please, comment on potential foreseen changes to manufacturing process, in-process controls, specifications and related analytical methods for the API and their validation.