EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2018
EMA/CHMP/668548/2018

CHMP List of outstanding issues

To be addressed by the active substance manufacturers for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group

Referral under Article 31 of Directive 2001/83/EC

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

Nationally authorised products: various

Centrally authorised products:
Amlodipine-Valsartan Mylan EMEA/H/A-31/1471/C/4037/0004; Aprovel EMEA/H/A-31/1471/C/141/0172; Coaprovel EMEA/H/A-31/1471/C/222/0187; Copalia EMEA/H/A-31/1471/C/774/0099; Copalia HCT EMEA/H/A-31/1471/C/1159/0069; Dafiro EMEA/H/A-31/1471/C/776/0101; Dafiro HCT EMEA/H/A-31/1471/C/1160/0070; Entresto EMEA/H/A-31/1471/C/4062/0021; Exforge EMEA/H/A-31/1471/C/716/0098; Exforge HCT EMEA/H/A-31/1471/C/1068/0068; Ifirmacombi EMEA/H/A-31/1471/C/2302/0020; Ifirmasta EMEA/H/A-31/1471/C/962/0018; Irbesartan Hydrochlorothiazide Zentiva EMEA/H/A-31/1471/C/783/0101; Irbesartan Teva EMEA/H/A-31/1471/C/1093/0032; Irbesartan Zentiva EMEA/H/A-31/1471/C/785/0080; Irbesartan/Hydrochlorothiazide Teva EMEA/H/A-31/1471/C/1112/A31/0041; Karvea EMEA/H/A-31/1471/C/142/0175; Karvezide EMEA/H/A-31/1471/C/221/0188; Neparvis EMEA/H/A-31/1471/C/4343/0020

Active substances: candesartan, irbesartan, losartan, olmesartan, valsartan

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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.

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

On 16 July, the CHMP adopted Lists of questions to MAHs and API manufacturers.

During the referral procedure, it became apparent that NDMA has also been found in APIs from other manufacturers, including Zhejiang Tianyu.

In addition, a further N-nitroso impurity N-nitrosodiethylamine (NDEA) has been found in earlier valsartan batches manufactured by ZH, and more recently also in a batch of losartan manufactured by Hetero Labs, India(confidential information deleted).

According to the principles of ICH M7, these nitrosamines found in APIs and corresponding finished products are of concern, and compound-specific risk assessments to derive acceptable daily intakes associated with a theoretical excess cancer risk of not more than 1 in 100000, were performed. CHMP currently considers daily intake of 96 ng/d for NDMA and 26.5 ng/d for NDEA associated with this risk level. This would correspond to 0.3 ppm for NDMA and 0.08 ppm for NDEA in valsartan 320 mg tablets. The acceptable daily intake levels from other sartans will depend on the maximum daily dose and can be derived from this.

The questions below adopted by CHMP on 20 September 2018 are for valsartan a consequence of the assessment of responses from stakeholders and other data that became available. As the scope has been widened to include all sartans marketed in EU with a tetrazole moiety in their molecular structure due to the above findings, new questions are addressed to MAHs and API manufacturers for those sartans.

Questions

The API manufacturers should be aware of the risk of potential nitrosamine formation resulting from the quenching process for residual azide and are strongly recommended to separate the quenching process from drug substance synthesis in future. Based on the data available so far, the generation of nitrosamines can be reduced/avoided if the aqueous waste phase separated from the organic phase is quenched with $NaNO_2$/HCl, while the organic phase (containing the product) is washed with H_2O to remove unreacted azide.

The API manufacturers with sartans are therefore requested to disclose how they deal with excess of azide in the synthesis of drug substance or starting material(s). This step is usually companied with addition of $NaNO_2$ and thus, detailed knowledge of this procedure is absolutely necessary. Furthermore, API manufacturers should outline if the separation of aqueous phase that contains azide is controlled concerning the residual azide that is potentially genotoxic as well.

The API manufacturers of all APIs containing Valsartan, Losartan, Olmesartan, Irbesartan or Candesartan are requested to address the following questions:

To all API manufactures of Losartan, Olmesartan, Irbesartan, Candesartan, Valsartan with confirmed presence of nitrosamines in the API:

1. The manufacturer is requested to provide information on NDMA/NDEA (or any other nitrosamine if their formation is possible during synthesis) content in API batches manufactured for medicinal products authorised in the EU/EEA that are at risk of containing NDMA/NDEA or any other nitrosamine. The manufacturers should preferably use analytical methods developed by OMCLs (see https://www.edqm.eu/en/news/omcls-release-three-methods-determination-ndma-sartans).

2. If submitting data generated using methods not developed by the OMCLs, please provide details on:
   a) the analytical quantification method for detecting NDMA/NDEA in the API, 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 nitrosamine levels above the acceptable 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.

3. On the basis of responses to Q2, a risk assessment for NDEA and if applicable other N-nitrosamines contaminations in the APIs in scope of this referral, should be performed by Manufacturers, taking into account potentially additive or synergistic toxicological effects with NDMA.

To all other API manufacturers of Losartan, Olmesartan, Irbesartan, Candesartan and Valsartan:

4. The manufacturer is requested to conduct a thorough review of the manufacturing process(es) of the above active substance(s) with respect to the potential for N-nitrosamines impurities. In particular, information should be provided on the possible formation of N-nitrosamines during the process (NDMA and NDEA having already been found in sartan APIs). In this regard, it should be stated whether sodium nitrite is used at all in the process (it is often used to quench azide following tetrazole synthesis). If so, there is the potential for generation of N-nitrosamines when a secondary amine is also present in the reaction mixture. Secondary amines could originate from impurities in or degradants of solvents (e.g. DMF, DMA, NMP) or reagents (e.g. tertiary amine bases such as Et3N, etc.), or be present intentionally, e.g. as part of a raw material. The manufacturer should discuss the potential for formation of N-nitrosamines, and provide a detailed description of the relevant process step including quench, work-up, phase separation and extraction procedures as well as information on waste streams. Please provide information on whether you are currently using (or have in the past used) any step in the API manufacturing process that may potentially lead to the generation of nitrosamine impurities.

5. If there is any potential for formation of N-nitrosamines, you are requested to provide details on:
   a) when was this process introduced for the manufacture of API (or for how long it has been used, if in the past);

   b) what levels of nitrosamines are expected in batches of API. Please provide the full details of the analytical method(s), including the method validation(s). The manufacturers should preferably use analytical methods used by OMCLs mentioned above.

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

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

e) any proposed corrective and preventive actions to ensure that the manufacturing process does not generate *N*-nitrosamines. Please comment on potential foreseen changes to manufacturing process, in-process controls, specifications and related analytical methods for the API and their validation.

6. On the basis of responses to Q 5, a risk assessment for NDEA and if applicable other N-nitrosamines contaminations in the APIs in scope of this referral, should be performed by manufacturers, taking into account potentially additive or synergistic toxicological effects with NDMA.

Questions to specific API manufacturers for Valsartan in reference to the provided responses:

(confidential information deleted)