



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2018
EMA/CHMP/668547/2018

CHMP List of outstanding issues

to be addressed by the marketing authorisation holders 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



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

MAHs are reminded of their obligations in accordance with requirements in Directive 2001/83/EC and its Annexes to ensure that the quality of each batch of their finished product is fully satisfactory, even for drug substance quality. Therefore, the MAHs are requested to properly address the control strategy on NDMA/NDEA and other N-nitrosoamines within the timeframe of this procedure.

The API manufacturers and MAHs should be aware of the risk of potential nitrosamine formation resulting from the quenching process for residual azide and it is 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 NaNO₂/HCl, while the organic phase (containing the product) will be washed with H₂O to remove unreacted azide.

Of note, the API manufacturers with sartans are requested by CHMP (see separate LoOI) to disclose how they deal with excess of azide in the synthesis of drug substance or starting material(s). This step is usually accompanied with addition of NaNO₂ and thus, detailed knowledge of this procedure is absolutely necessary. Furthermore, API manufacturers are requested to outline if the separation of aqueous phase that contains azide is controlled concerning the residual azide that is potentially genotoxic as well.

The MAHs of all products containing Valsartan, Losartan, Olmesartan, Irbesartan or Candesartan are requested to address the following questions:

1. The MAH is requested to conduct a thorough review of the manufacturing process(es) of the above active substance(s) used in its finished products with respect to the potential for N-nitrosamine 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 MAH 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 state if you are currently using (or have previously used) any API supplier that has steps in the API manufacturing process that may potentially lead, or have led, to the generation of NDMA, NDEA or any other possible N-nitroso impurity.
2. If there is any potential for formation of N-nitrosamines, you are requested to provide details on:
 - a) the time period when this(ese) supplier(s) has(ve) been used and its impact on final product batches released to the European market, including figures on sales and patient exposure of product containing NDMA, NDEA or any other N-nitroso impurity (potential or confirmed) in EU/EEA member states;
 - b) data in the annexed table on the use in clinical practice including information on indication, dose, and duration of treatment;
 - c) what levels of NDMA/NDEA or any other N-nitroso impurity are/were present in your finished product(s). You should preferably use analytical methods used by OMCLs (see <https://www.edqm.eu/en/news/omcls-release-three-methods-determination-ndma-sartans>), and if not, full details of the analytical methods, including the method validation should be provided.
 - d) 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 and validation;
 - e) a calculation of an acceptable daily intake levels of NDMA/NDEA or any other possible N-nitroso impurity should be performed, considering the framework described in ICH M7 as applicable to the class of nitrosamines.

- f) In relation to the above, any proposed corrective and preventive actions to ensure that the finished product does not contain *N*-nitrosamines. Please comment on potential foreseen changes to in-process controls, specifications and related analytical methods for the finished product and their validation.
3. On the basis of responses to question 2 above, a risk assessment for NDEA and if applicable other N-nitrosamine contaminations in the products in scope of this referral, should be performed by MAHs, taking into account potentially additive or synergistic toxicological effects with NDMA.

Questions specific to individual Valsartan MAHs

(confidential information deleted)

Annex

INN	Product name	Indications	Pharmaceutical forms and strengths	Doses (as approved and used in clinical practice)	Treatment duration (as approved and used in clinical practice)