16 July 2018
EMA/CHMP/467845/2018

CHMP List of questions

To be addressed by the marketing authorisation holders for valsartan-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC

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

Amlodipine-Valsartan Mylan EMEA/H/A-31/1471/C/4037/0004
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
Neparvis EMEA/H/A-31/1471/C/4343/0020

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 compounds.

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

2. Questions

The marketing authorisation holders (MAHs) of valsartan-containing medicinal products are requested to address the following questions:

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 state if you are currently using (or have previously used) any API supplier (Zhejiang Huahai or others) that have steps in the valsartan manufacturing process that may potentially lead, or have led, 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) 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 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 NDMA levels are/were present in your finished product(s). If finished product batches have been tested, provide full details of the analytical methods used, including their validation;

d) 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;

e) a calculation of NDMA acceptable daily intake levels 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 levels above an acceptable daily intake. Please comment on potential foreseen changes to in-process controls, specifications and related analytical methods for the finished product and their validation.

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)