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EDQM's actions to evaluate impact of impurity in active substance valsartan

The European Directorate for the Quality of Medicines & HealthCare (EDQM) is aware of a quality defect related to an impurity in the active substance valsartan used in medicines to treat high blood pressure marketed in Europe. Traces of the impurity N-nitrosodimethylamine (NDMA), a substance classified as probable human carcinogen, were discovered in one specific source of valsartan, manufactured by Zhejiang Huahai Pharmaceuticals, which supplies manufacturers of medicinal products worldwide. Patients are advised to speak to their doctor for further instructions and to continue their treatment.

NDMA is an unexpected impurity that was not detected by routine tests carried out by the manufacturer. While the exact level of the contamination is still being investigated, competent authorities throughout the world have recalled batches of valsartan-containing medicines as a precautionary measure and have informed healthcare professionals and relevant prescribers of this action.

Earlier this month, a pan-European alert system has been triggered by the European Medicines Agency (EMA) in order to assess the extent of this incident and to establish remedial action plans.

The EDQM is part of this pan-European alert system and is actively working with the EMA and national competent authorities to better understand the potential impact of this impurity and the extent of the issue.

With regards to this investigation, the EDQM has taken a number of actions:

- The immediate suspension of the Certificate of suitability held by Zhejiang Huahai Pharmaceuticals. The manufacturer and Competent Authorities in Europe and international partners have been informed of this suspension;
- Request to the concerned manufacturer to eliminate or reduce the impurity to an acceptable level in future batches;
- Thorough review of manufacturing data submitted by other manufacturers of valsartan and other structurally related active substances in order to determine whether or not they have a comparable route of synthesis and whether their active substance is NDMA-free
- Coordination of the activities of a group of Official Medicines Control Laboratories from member states to test NDMA in samples of active substances and medicinal products which are on the market in Europe.

The EDQM is doing its utmost to understand the root cause of this contamination and to reduce the impact of the issue on patients' health.

The EDQM will communicate further, as soon as more information on the matter becomes available. For more information, follow us on www.edqm.eu.

Background:

The so-called "Certificate of suitability" (or CEP) procedure of the EDQM is one out of three alternative options that can be used by a manufacturer to demonstrate that the quality of their active substance is suitably controlled by the respective monograph of the European Pharmacopoeia, and is in compliance with the current regulatory requirements. To obtain a certificate, the manufacturer may submit an application to the EDQM describing the manufacturing process and the methods applied for the quality control, including for the control of impurities. The data are assessed by experienced quality assessors nominated by National Competent Authorities and EDQM. Following a positive conclusion of the assessors, the EDQM grants a CEP. A copy of the CEP can then be used in any marketing authorisation application (MAA) for a medicinal product in which the active substance from this specific source is included.

Alternatively, the same data can be filed either in an Active Substance Master File (ASMF), to be submitted to each competent authority, or in the active substance part of the quality dossier of the MAA.

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Note for the Editor: Further information is available on the internet site **https://www.edqm.eu/**
The EDQM is a leading organisation that protects public health by enabling development, supporting implementation, and monitoring the application of quality standards for safe medicines and their safe use. Our standards are recognised as a scientific benchmark worldwide. The European Pharmacopoeia is legally binding in member states[1]. Similarly, the EDQM develops guidance and standards in the areas of blood transfusion, organ transplantation and consumer health issues.

[1]There are thirty-nine members of the European Pharmacopoeia Commission: *Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland , France , Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Republic of Moldova, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey, Ukraine, United Kingdom and the European Union.*

A political organisation set up in 1949, the Council of Europe works to promote democracy and human rights continent-wide. It also develops common responses to social, cultural and legal challenges in its 47 member states.