17 October 2018, Strasbourg, France

Update on the review of CEP applications for sartans and the availability of test methods for nitrosamines

Following the detection of the impurity NDMA (N-nitrosodimethylamine) in valsartan at the end of June, the EDQM has conducted a complete review of the manufacturing information submitted in all Certificate of suitability (CEP) applications for valsartan and other structurally related active substances. The EDQM contacted those manufacturers of valsartan and other sartans holding CEPs which might have presented a risk of contamination with nitrosamines, including NDMA and NDEA (N-nitrosodiethylamine). Both contaminants are classified as probable human carcinogens (substances that may cause cancer).

Since taking action for those substances that were at greatest risk of contamination, the EDQM has continued to assess the data received from all manufacturers concerned and to ensure that appropriate controls are put in place. Evaluation of the data received is prioritised on the basis of risks. Once assurance has been obtained that there is no risk of contamination (if needed, after an additional request for information), the EDQM issues either a letter confirming that the review of the CEP application has been completed or a revised CEP.

NDMA and NDEA have been detected in valsartan manufactured by Zhejiang Huahai Pharmaceutical and the CEP for this valsartan was suspended in July 2018 (as soon as the EDQM was informed of the presence of NDMA in the substance), thus stopping the reference to this CEP in marketing authorisations for medicinal products in Europe and countries accepting CEPs and hence forbidding the use of this source of valsartan in related medicines.

An inspection carried out jointly by EU authorities and the EDQM in September 2018 found that Zhejiang Huahai Pharmaceutical did not comply with Good Manufacturing Practice (GMP) for the manufacture of valsartan at their Chuannan site in Linhai, China. Several deficiencies were found, including in the way the company investigated the presence of NDMA and NDEA in their valsartan product. A statement of non-compliance for the manufacture of valsartan has since been published on the EudraGMDP website. Zhejiang Huahai Pharmaceutical also manufactures intermediates for valsartan which are supplied to other manufacturers. As a result of the GMP non-compliance, Zhejiang Huahai intermediates can no longer be used for the manufacture of valsartan, and as a consequence 4 CEPs for valsartan have been revised by the EDQM in order to remove reference to this manufacturing site.

Low levels of NDEA have been detected in losartan manufactured by Hetero Labs; according to available data, these levels remain below the currently acceptable amounts established for this impurity. Further investigations are on-going to determine the extent of the contamination. Some low levels of NDEA have also been found in irbesartan manufactured by Aurobindo Pharma Limited with, in some batches, levels exceeding the acceptable amounts. Consequently, on 8 October 2018 the CEP has been suspended until corrective action has been taken by the manufacturer and verified by the EDQM.

The EDQM is coordinating a risk–oriented sampling and testing programme carried out by the European Network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans. As part of this programme, the Network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products.

In addition to the 3 analytical methods for the determination of NDMA published earlier, the OMCLs Network recently extended its efforts to developing methods for the specific testing of NDEA in sartans. The first method for simultaneous determination of NDMA and NDEA in sartan tablets, developed and validated for valsartan tablets, has been released by the German OMCL, the CVUA

Karlsruhe. It is based on the principle of UHPLC-APCI-MS/MS and allows determining both contaminants simultaneously. More detail on this new method can be found here.

The EDQM continues to work closely with the European Medicines Agency (EMA), national authorities and other international partners in order to share data, avoid duplication of work and ensure patients are protected from any risk of contamination.

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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.*

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