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Update on review of valsartan medicines

Risk from NDMA remains low, a related substance NDEA also being investigated

The European Medicines Agency (EMA) has updated its calculation of the risk from valsartan medicines containing N-nitrosodimethylamine (NDMA), taking into account results from latest tests on the active substance from Zhejiang Huahai.

In line with EMA's previous assessment, the life-time risk of cancer is considered low and is estimated to be in the order of 1 in 5,000 for an adult patient who had taken an affected valsartan medicine at the highest dose (320 mg) every day from July 2012 to July 2018.

EMA's risk assessment is based on the average levels of NDMA in the active substance produced by Zhejiang Huahai since 2012 (when the company changed its manufacturing process) and on the assumption that all the NDMA is transferred to the final product.

Patients who have taken treatments with lower doses or for shorter lengths of time will be at a lower risk. The risk will also be lower for patients who have taken valsartan produced by Zhejiang Tianyu, which had smaller amounts of NDMA than valsartan produced by Zhejiang Huahai.

The low risk estimate is to some extent supported by a Danish study[1] which tracked patients who had taken medicines containing valsartan from Zhejiang Huahai over the past 6 years. However, the authors note that patients were followed up for a relatively short period (4.6 years on average).

In addition to NDMA, EMA is assessing the impact of a related substance, N-nitrosodiethylamine (NDEA), which has been detected in valsartan made by Zhejiang Huahai using its previous manufacturing process before changes were introduced in 2012. Both NDEA and NDMA belong to the class of nitrosamines and are classified as probable human carcinogens (substances that could cause cancer).

Data on levels of NDEA are currently very limited, and EMA will provide further information on whether its presence impacts the risk assessment once more information becomes available.

Although the review covers all valsartan medicines, the immediate focus has been on medicines containing the active substance manufactured by Zhejiang Huahai and Zhejiang Tianyu where unacceptable levels of NDMA have been confirmed. EU authorities have now carried out inspections of the manufacturing sites of both companies in China and will consider the findings.

[1] Pottegard A, Kristensen K, Ernst MT, Johansen NB, Quartorolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ 2018;362:k3851.

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Medicines containing valsartan from Zhejiang Huahai and Zhejiang Tianyu are no longer being distributed in the EU or have been recalled. Both companies are not currently authorised to produce valsartan for medicines in the EU.

EMA continues to work closely with national authorities, international partners and EDQM to gather the necessary information which would allow the Agency to have a better understanding of why impurities were present in the active substance in the first place.

Based on the final outcome of the review, authorities in the EU will take necessary measures to ensure that similar problems do not occur in future.

More about the medicine

Valsartan is an angiotensin-II-receptor antagonist used to treat hypertension (high blood pressure), recent heart attack and heart failure. It is available on its own or in combination with other active substances.

Medicines containing valsartan as the only active substance have been authorised in the EU via national authorities. Nine products containing valsartan in combination with other active substances have been authorised centrally via EMA.

More about the procedure

The review of valsartan medicines was triggered by the European Commission on 5 July 2018 under Article 31 of Directive 2001/83/EC.

The review is being carried out by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion. The CHMP opinion will then be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.