Update to Safety Circular P17_2018
EMA's review on Valsartsan-containing products extended to other sartan medicines

05.11.2018 | Circular Number P19/2018

Information on sartan medicines

- Candesartan, irbesartan, losartan, olmesartan and valsartan belong to a class of medicines known as angiotensin-II-receptor antagonists (also known as sartans);
- The medicines are used to treat patients with hypertension (high blood pressure) and those with heart failure or who have had a recent heart attack. They work by blocking the action of angiotensin II, a hormone that constricts blood vessels and causes blood pressure to rise.

Information from the EMA about the ongoing review on sartan medicines

On 5th July 2018, the Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (EMA) started a review of medicines containing valsartan. On 20th September 2018 the review was extended to include medicines containing candesartan, irbesartan, losartan and olmesartan.
The reviews were triggered by the European Commission, under Article 31 of Directive 2001/83/EC.

The reviews on sartan medicines were triggered due to impurities detected in the sartan active substances:

- N-nitrosodimethylamine (NDMA) was detected in the valsartan active substance supplied by the Zhejiang Huahai Pharmaceutical to EU manufacturers;
- N-nitrosodiethylamine (NDEA) was detected in the losartan active substance made by Hetero Labs in India.

Based on animal studies, both NDEA and NDMA belong to the class of nitrosamines and are classified as probable human carcinogens (substances that could cause cancer). How these impurities came to be present during the manufacture of sartans is yet to be fully established and is being evaluated in the ongoing review.

Medicines containing valsartan made by Zhejiang Huahai in China have been recalled by national authorities. Medicines containing valsartan from another company Zhejiang Tianyu are no longer being distributed in the EU. Valsartan-containing medicines manufactured by Zhejiang Huahai and Zhejiang Tianyu were confirmed to contain unacceptable levels of NDMA and therefore are no longer available in the EU market.

Based on the trace amounts of NDEA seen so far in one batch of losartan from Hetero Labs, there is **no immediate risk to patients**. However, data on levels of NDEA are currently very limited, and the EMA will provide further information on whether its presence impacts the risk assessment once more information becomes available.

On the 8th October 2018 the Indian company Aurobindo Pharma was prevented from supplying medicines containing Irbesartan in the EU, due to low levels of NDEA found. The review into the presence of impurities in sartans and their potential effects in patients is ongoing.

The EMA has updated a calculation of the risk from valsartan medicines containing NDMA, considering results from latest tests on the active substance from Zhejiang Huahai. Patients who have taken treatments with lower doses or for shorter lengths of time will be at a lower risk (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). The risk is lower for patients who have taken valsartan produced by Zhejiang Tianyu, which had smaller amounts of NDMA than valsartan produced by Zhejiang Huahai.

The EMA review is investigating:

- The root causes for the presence of NDMA and NDEA in sartan medicines;
- The possible impact on patients who have been taking sartan medicines;
- Measures to reduce or eliminate the impurity from future batches produced by the companies;
- Whether other sartan medicines may be affected.

Following the review, 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.

For more information on the sartan medicines review please see the European Medicines Agency's webpage on the Sartan medicines Referral and Sartans Press Release

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on sartan medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from: http://www.medicinesauthority.gov.mt/adrportal) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to postlicensing.medicinesauthority@gov.mt or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Security marking: Public

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this formt (address side up), stapling the ends and then posting (no stamp required)

Feedback:

We thank you for your interest and look forward to hearing your opinion.

Postage will be paid
by the Licensee

No postage stamp
necessary if posted
in Malta and Gozo

BUSINESS REPLY SERVICE
Licence no. 656

Pharmacovigilance Section

Post-Licensing Directorate

Medicines Authority

Sir Temi Żammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000