Nitrosamines: recommendations for sartans aligned with those for other medicines by EMA

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Information on Sartans

- Sartans are also known as angiotensin-II receptor antagonists. Sartans included in this review are candesartan, irbesartan, losartan, olmesartan and valsartan.
- Sartans are used for treating patients with hypertension (high blood pressure) and with certain heart and kidney diseases
- Sartans work by blocking action of a hormone called angiotensin-II which constricts blood vessels and causes blood pressure to rise
- Sartans have a tetrazole ring which is a specific ring structure whose synthesis could potentially lead to forming a nitrosamine impurity
- Azilsartan, eprosartan and telmisartan were not included in this review because they do not have a tetrazole ring.

Information from the EMA about the review on Sartan medicines

On 5th July 2018, the Committee for Medicinal Products for Human Use (CHMP), started a review of valsartan medicines. The reviews on sartans were triggered due to impurities N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) detected in valsartan and losartan active substances respectively.

On 20th September 2018, medicines containing candesartan, irbesartan, losartan and olmesartan were also included in the review. Nitrosamines are classified as substances that probably cause cancer (human carcinogens). These impurities were either not found or were present at very low amount in the vast majority of Sartans. Recommendations to limit the impurities caused by nitrosamine in Sartas, have been aligned with those issued for other classes of medicines by the CHMP. The limits for nitrosamine previously applied to the active ingredients but this has been changed and will apply to the finished products (eg tablets). As per internationally agreed standards (ICH M7(R1)), the limits are to ensure that the excess risk of cancer from nitrosamines in any Sartans is below 1 in 100,000 for a person taking the medicine indefinitely.

In line with previous recommendations:

- Appropriate control strategies should be in place by companies. These are done to prevent or limit the presence of nitrosamine impurities as much as possible and also to improve their manufacturing processes where necessary
- The risk of nitrosamine present in the medicines should be evaluated by companies by carrying out appropriate tests.

In January 2019, the review of Sartans was concluded by the CHMP. A wider review was eventually conducted by the committee by also considering the experience from sartans and other medicines where nitrosamines were detected. Companies need to fulfil the revised and updated conditions for Sartans and this brings them in line with those for other classes of medicines. EMA will continue working with national authorities and the EC to ensure that all companies are taking the necessary measures. The close cooperation between EMA and the European Directorate for the Quality of Medicines & HealthCare and international partner agencies will continue.

For more information visit the European Medicines Agency's webpage on Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group.

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 and sending it to Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or online to **http://www.medicinesauthority.gov.mt/adrportal** 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.

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)

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