Sartans manufacturing to be reviewed by companies to avoid presence of nitrosamine impurities

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Information on Sartan medicines

- Candesartan, irbesartan, losartan, olmesartan and valsartan belong to a class of medicines called sartans (also known as angiotensin-II-receptor antagonists)
- These medicines are used to treat patients with hypertension (high blood pressure) and those with certain heart or kidney diseases. They work by blocking the action of angiotensin II, a hormone that constricts blood vessels and causes blood pressure to rise
- These sartan medicines have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of nitrosamine impurities. Other medicines of the class which do not have this ring, such as azilsartan, eprosartan and telmisartan, were not included in the review

Information from the EMA about the review on Sartan medicines

Following EMA's review on N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA), classified as probable human carcinogens, impurities were either not found or present at very low levels. in most of Sartan medicines.

The highest possible cancer risk with these impurities was estimated during the review. The estimated risk for 100,000 patients taking valsartan from Zhejiang Huahai (where the highest levels of impurities were found) every day for 6 years at the highest dose, was of 22 extra cases of cancer due to NDMA over the lifetimes. NDEA in these medicines could lead to 8 extra cases in 100,000 patients taking the medicine at the highest dose every day for 4 years.[1]

The estimates have been extrapolated from animal studies and are very low compared with the lifetime risk of cancer in the EU (1 in 2). EMA's recommendations are:

- Companies that make sartan medicines (also known as angiotensin II receptor blockers) are being required to review their manufacturing processes so that they do not produce nitrosamine impurities
- Companies will have a transition period to make any necessary changes, during which strict temporary limits on levels of these impurities will apply. After this period, companies will have to demonstrate that their sartan products have no quantifiable levels of these impurities before they can be used in the EU
- Companies must now take measures to avoid the presence of these impurities and carry out rigorous testing of their products.

[1] The 6 and 4 years refer to the duration of time NDMA and NDEA are believed to have been present in valsartan from Zhejiang Huahai

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

In Malta

For Healthcare Professionals

- Nitrosamines are potent carcinogens in animals and probable carcinogens in humans
- These impurities can form during the production of sartans that contain a tetrazole ring when certain reaction conditions are met or when contaminated materials are used
- For NDMA, the key step involves dimethylamine (DMA) which forms the impurity in the presence of nitrites, usually under acidic conditions. A similar step – involving diethylamine (DEA) – is linked to the presence of NDEA
- A rigorous testing regime is in place to ensure that sartan medicines are acceptably safe
- If there is a need for further recalls or other measures, national authorities will inform you of what action to take
- Manufacturers must now review their manufacturing processes to avoid the presence of nitrosamines

Advice for Patients

- There is a very low risk that nitrosamine impurities at the levels previously found in some sartan medicines could cause cancer in humans
- Ever since these impurities were first seen in some sartan medicines, regulatory authorities in the EU have been working to protect patients' health. Following tests, some medicines have been recalled from pharmacies and are no longer used in the EU
- EMA is now taking further action to prevent these impurities from being present in future batches of sartan medicines
- A rigorous testing regime is in place to ensure that sartan medicines are acceptably safe
- You should not stop taking any sartan medicines without speaking to your doctor
- If you have any questions about your medicine or any medicine you have taken in the past, speak to your doctor or pharmacist.

For more information on the sartan medicines review, please see the European Medicines Agency's webpage on the Sartan medicines Referral.

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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Pharmacovigilance Section

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