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Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities

On 31 January 2019, EMA recommended that companies making sartan blood pressure medicines (also known as angiotensin II receptor blockers) 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.

These recommendations follow EMA's review of N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), which are classified as probable human carcinogens (substances that could cause cancer) and have been detected in some sartan medicines.

For the vast majority of sartan medicines, impurities were either not found or were present at very low levels.

The review estimated the highest possible cancer risk with these impurities. It concluded that if 100,000 patients took valsartan from Zhejiang Huahai (where the highest levels of impurities were found) every day for 6 years at the highest dose, there could be 22 extra cases of cancer due to NDMA over the lifetimes of those 100,000 patients. 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).

How impurities came to be present in sartans

Before June 2018, NDMA and NDEA were not among the impurities identified in sartan medicines and were therefore not detected by routine tests.

It is now known that these impurities can form during the production of sartans that contain a specific ring structure known as a tetrazole ring under certain conditions and when certain solvents, reagents, and other raw materials are used. In addition, it is possible that impurities were present in some

[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

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sartans because manufacturers had inadvertently used contaminated equipment or reagents in the manufacturing process.

Companies must now take measures to avoid the presence of these impurities and carry out rigorous testing of their products.

Testing during and after the transition period

While the goal is to have no quantifiable nitrosamine impurities in sartans, interim limits have been set for NDMA and NDEA in line with current international guidelines.[2]

Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed in the EU.

The limits are based on the maximum daily intake for each impurity derived from animal studies: 96.0 nanograms for NDMA and 26.5 nanograms for NDEA. Dividing these by the maximum daily dose for each active substance gives the limit in parts per million (see Table 1).

The transition period, which will last for 2 years, will allow companies to make the necessary changes to their manufacturing processes and to put in place testing regimes able to detect the smallest amounts of these impurities.

After the transition period, companies must exclude the presence of even lower levels of NDEA or NDMA in their products (< 0.03 parts per million).

Table 1. Temporary limits for NDMA and NDEA impurities

	NDMA		NDEA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**	**Maximum daily intake (ng)**	**Limit (ppm)**
Candesartan (32 mg)	96.0	**3.000**	26.5	**0.820**
Irbesartan (300 mg)	96.0	**0.320**	26.5	**0.088**
Losartan (150 mg)	96.0	**0.640**	26.5	**0.177**
Olmesartan (40 mg)	96.0	**2.400**	26.5	**0.663**
Valsartan (320 mg)	96.0	**0.300**	26.5	**0.082**

Investigation continuing

EMA and national authorities will continue investigating the presence of nitrosamine impurities in medicines, including other impurities such as N-nitrosoethylisopropylamine (EIPNA), N-nitrosodiisopropylamine (DIPNA) and N-nitroso-N-methylamino butyric acid (NMBA).

Authorities in the EU will also consider the lessons that can be learned from this review to improve the way impurities in medicines are identified and handled.

EMA's recommendations for NDMA and NDEA were sent to the European Commission, which issued a legally binding decisions. An assessment report with further details about the review has been published on EMA's website.

[2] International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidance: M7(R1)

Information 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. You can also contact your national medicines authority.

Information 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.

More about the medicine

The review concerns candesartan, irbesartan, losartan, olmesartan and valsartan, which belong to a class of medicines called sartans (also known as angiotensin-II-receptor antagonists).

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.

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.

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. On 20 September 2018, the review was extended to include medicines containing candesartan, irbesartan, losartan and olmesartan.

The review was carried out by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion was forwarded to the European Commission, which issued final legally binding decisions for the medicines concerned between 2 April and 17 April 2019 that are applicable in all EU Member States.