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Nitrosamines: EMA aligns recommendations for sartans with those for other medicines

On 12 November 2020, EMA's human medicines committee (CHMP) aligned recommendations for limiting nitrosamine impurities in sartan medicines with previous recommendations it issued for other classes of medicines.

The main change concerns the limits for nitrosamines, which previously applied to the active ingredients but will now apply instead to the finished products (e.g. tablets). These limits, based on internationally agreed standards (ICH M7(R1)), should ensure that the excess risk of cancer from nitrosamines in any sartan medicines is below 1 in 100,000 for a person taking the medicine for lifelong treatment.

In line with previous recommendations, companies should have appropriate control strategies to prevent or limit the presence of nitrosamine impurities as much as possible and, where necessary, improve their manufacturing processes. Companies should also evaluate the risk of nitrosamines being present in their medicines and carry out appropriate tests.

Nitrosamines are classified as probable human carcinogens (substances that could cause cancer). In the vast majority of sartan medicines, these impurities were either not found or were present at very low levels.

The CHMP concluded its review of sartan medicines in January 2019. The committee subsequently conducted a wider review, taking into account the experience from sartans and other medicines where nitrosamines were detected. The revised conditions companies need to fulfil for sartans brings them in line with those for other classes of medicines issued in June 2020.

EMA will continue working with national authorities and the European Commission to ensure that companies are taking all necessary measures. EMA will also continue its close cooperation with the European Directorate for the Quality of Medicines & HealthCare and international partner agencies.

More about the medicine

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

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These sartan medicines have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of nitrosamine impurities. Other sartan medicines which do not have this ring, such as azilsartan, eprosartan and telmisartan, were not included in this review but are covered by the subsequent review of other medicines.

Sartans 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

A review of valsartan medicines started on 5 July 2018 at the request of European Commission, 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), which is responsible for questions concerning medicines for human use and adopted the Agency's opinion. The CHMP opinion was forwarded to the European Commission, which issued legally binding decisions between 2 and 17 April 2019 that are applicable in all EU Member States.

The recommendations from this review have now been updated and aligned with those of the Article 5 (3) procedure, which concluded on June 2020. The updated recommendations were also forwarded to the European Commission, which issued final legally binding decisions between 12 February and 19 February 2021 applicable in all EU Member States.