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EU authorities take further action in ongoing review of sartans

Zheijiang Huahai placed under increased supervision; Aurobindo Pharma stopped from supplying irbesartan to the EU

EU authorities are placing the Chinese company Zheijiang Huahai under increased supervision following European and US inspections which revealed weaknesses in quality management at the company's Chuannan site in Linhai, China.

The inspection findings included deficiencies in the way the company investigated impurities in its valsartan products and led EU authorities to issue a statement of non-compliance with Good Manufacturing Practice (GMP), prohibiting the use of its valsartan in EU medicines.

This latest action means that EU authorities will supervise the manufacture of other active substances produced by Zhejiang Huahai more closely.

Authorities will monitor corrective measures being implemented by the company on a regular basis and increase the frequency of inspections of the site. In addition, marketing authorisation holders for EU medicines will be required to perform additional tests on all active substances supplied by Zhejiang Huahai.

In July 2018, the detection of impurities – N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) – in valsartan from Zhejiang Huahai led to an EU-wide review of all valsartan medicines. The review was subsequently extended to other 'sartan' medicines when very low levels of NDEA were found in losartan made by Hetero Labs in India.

Both NDMA and NDEA, which have not been found in any of Zheijiang Huahai's other products, are classified as probable human carcinogens (substances that could cause cancers). A preliminary risk assessment for NDMA in valsartan indicated that the lifetime risk of cancer is low.

Aurobindo Pharma stopped from supplying irbesartan to the EU

Low levels of NDEA have now also been found in a third sartan, irbesartan, made by another Indian company, Aurobindo Pharma. On 8 October 2018, the European Directorate for the Quality of Medicines & HealthCare (EDQM) suspended Aurobindo Pharma's CEP,[1] effectively stopping the supply in the EU of medicines containing irbesartan from this company.

[1] CEP: certificate of suitability to the monographs of the European Pharmacopoeia

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National authorities in the EU are currently considering whether to recall medicines containing Aurobindo Pharma's irbesartan from pharmacies as a precaution.

The review into the presence of impurities in sartans and their potential effects in patients is ongoing. EMA will continue working with national authorities, international partners and EDQM and will provide updates as more information becomes available.

More about the medicines

The ongoing review is evaluating candesartan, irbesartan, losartan, olmesartan and valsartan, which 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.

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 is being carried out by EMA's Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion. 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.