

European Union: Update on review of valsartan medicines. Risk from NDMA remains low, a related substance NDEA also being investigated.

The European Medicines Agency (EMA) has updated its calculation of the risk from valsartan medicines containing N-nitrosodimethylamine (NDMA), taking into account results from latest tests on the active substance from Zhejiang Huahai.

In line with EMA's previous assessment, the life-time risk of cancer is considered low and is estimated to be in the order of 1 in 5,000 for an adult patient who had taken an affected valsartan medicine at the highest dose (320 mg) every day from Jul 2012 to Jul 2018. EMA's risk assessment is based on the average levels of NDMA in the active substance produced by Zhejiang Huahai since 2012 (when the company changed its manufacturing process) and on the assumption that all the NDMA is transferred to the final product. Patients who have taken treatments with lower doses or for shorter lengths of time will be at a lower risk. The risk will also be lower for patients who have taken valsartan produced by Zhejiang Tianyu, which had smaller amounts of NDMA than valsartan produced by Zhejiang Huahai. The low risk estimate is to some extent supported by a Danish study which tracked patients who had taken medicines containing valsartan from Zhejiang Huahai over the past 6 years. However, the authors note that patients were followed up for a relatively short period (4.6 years on average).

In addition to NDMA, EMA is assessing the impact of a related substance, N-nitrosodiethylamine (NDEA), which has been detected in valsartan made by Zhejiang Huahai using its previous manufacturing process before changes were introduced in 2012. Both NDEA and NDMA belong to the class of nitrosamines and are classified as probable human carcinogens (substances that could cause cancer). Data on levels of NDEA are currently very limited, and EMA will provide further information on whether its presence impacts the risk assessment once more information becomes available.

Although the review covers all valsartan medicines, the immediate focus has been on medicines containing the active substance manufactured by Zhejiang Huahai and Zhejiang Tianyu where unacceptable levels of NDMA have been confirmed. EU authorities have now carried out inspections of the manufacturing sites of both companies in China and will consider the findings. Medicines containing valsartan from Zhejiang Huahai and Zhejiang Tianyu are no longer being distributed in the EU or have been recalled. Both companies are not currently authorised to produce valsartan for medicines in the EU.

Please refer to the following website in EMA for details:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/09/news_detail_003015.jsp&mid=WC0b01ac058004d5c1

In Hong Kong, there are 83 registered pharmaceutical products containing valsartan, and all products are prescription-only medicines.

A public announcement was issued on 6 Jul 2018 on the issue, and letters to inform local healthcare professionals of the latest development, including the affected products, recommendations on drug use and possible risk, were issued by the Department of Health (DH) on 6 Jul 2018, 9 Jul 2018, 25 Jul 2018 and 3 Aug 2018. Related news was also previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 6 Jul 2018, with the latest update posted on 11 Sep 2018.

In summary, there are four manufacturers, namely Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu in China and Hetero Labs Limited in India, reported to have detection of trace amounts of NDMA in the valsartan Active Pharmaceutical Ingredient (API) by various overseas drug regulatory authorities.

The DH contacted the certificate holders of all registered valsartan products to follow up on the local impact regarding valsartan API produced by the above mentioned manufacturers.

For API produced by Zhejiang Huahai, there are 5 affected products marketed in Hong Kong. The DH instructed the certificate holders to recall all the products from the market as a precautionary measure on 6 Jul 2018, and the DH noted that all the recalls have been completed. The affected products are:

| Product | Hong Kong Registration Number | Registration certificate holder |
|----------------------------------|-------------------------------|---------------------------------|
| Valtensin 160mg tablets | HK-61786 | Actavis Hong Kong Limited |
| Valtensin 80mg tablets | HK-61787 | Actavis Hong Kong Limited |
| Valtensin HCT tablets 160/12.5mg | HK-61784 | Actavis Hong Kong Limited |
| Valtensin HCT tablets 80/12.5mg | HK-61785 | Actavis Hong Kong Limited |
| Valsartan Stada 80mg tablets | HK-60794 | Hong Kong Medical Supplies Ltd |

For API produced by Zhejiang Tianyu, amongst the registered pharmaceutical products containing valsartan, there is only one product namely Retoni Tablets 80mg (HK-65604) registered by Swiss Pharmaceutical Co Limited (Swiss Pharmaceutical) which has used API produced by Zhejiang Tianyu and is available in the local market. As confirmed with Swiss Pharmaceutical, the API was tested by the Taiwan Food and Drug Administration (TFDA) and the company has not received any notice from the TFDA for NDMA contamination. The DH collected samples of Retoni tablets for analysis and no NDMA was detected.

For API produced by Zhuhai Rundu and Hetero Labs Limited, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by Zhuhai Rundu or Hetero Labs Limited.

According to the above EMA's announcement on the detection of the second impurity of NDEA in

the API produced by Zhejiang Huahai, there should be no local impact as all valsartan products manufactured using API produced by Zhejiang Huahai have been recalled from the market. The DH will keep vigilant on any further updates on the matter issued by overseas regulatory authorities.

So far, the DH has not received any adverse reactions related to the above products affected by the recall.

Patients who are taking the above products should not stop taking the medicines, but should seek advice from their healthcare professionals as soon as possible for proper arrangement.

Ends/Friday, Sep 14, 2018

Issued at HKT 16:00