

**The United States: FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products**

The US Food and Drug Administration (FDA) is updating the public on the agency's ongoing investigation surrounding the recent voluntary recall of several drug products containing the active pharmaceutical ingredient (API) valsartan, used to treat high blood pressure and heart failure.

The FDA's latest testing of products shows an additional unexpected impurity in three lots of Torrent Pharmaceuticals' recalled valsartan drug products. This second impurity, N-nitrosodiethylamine (NDEA) is a known animal and suspected human carcinogen. These Torrent products were included in the company's recall on 23 Aug 2018.

The FDA and the European Medicines Agency have learned that Zhejiang Huahai Pharmaceuticals (ZHP) found NDEA in several batches of its valsartan API. The FDA immediately began retesting all valsartan API and products, including both recalled products and those currently marketed in the US, for NDEA. Based on FDA testing to date, the agency discovered NDEA in some of ZHP's valsartan API. This impurity was also found in Torrent's valsartan 160mg (lot BV47D001) and 320mg (lots BV48D001 and BV48D002) tablets, which were made using API from ZHP and were part of the earlier recall. The FDA's testing shows that not all products made using ZHP valsartan API contain the NDEA impurity.

The FDA is continuing to test all products that contain valsartan for NDEA and related impurities. If the agency finds NDEA in products that have not been recalled, the FDA will work with companies to ensure all affected products are removed from the market. The agency is also evaluating the risks NDEA in these products poses to patients. The FDA expects to complete this risk analysis in the coming days and will continue to provide updates to the public as new information becomes available.

Please refer to the following website in FDA for details:

<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620499.htm>

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 FDA'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.

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