NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by the European Commission:

Product Name(s) in the Referring Member State, if applicable	See Annex I
Active substance(s)	Valsartan
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Applicant(s)/Marketing Authorisation Holder(s) in the referring Member State	Various – see Annex I

Valsartan is an angiotensin-II-receptor antagonist authorised in the EU as a single agent or in combination with other active substances and indicated for the treatment of hypertension, recent heart attack and heart failure.

The EU authorities were notified on the 22nd June 2018 that an Active Pharmaceutical Ingredient (API) manufacturer (Zhejiang Huahai Pharmaceutical, China) has detected the presence of a previously undetected impurity, N-nitrosodimethylamine (NDMA, also known as dimethylnitrosamine) in the valsartan API manufactured at its site in Chuannan. Zhejiang Huahai is one of the API manufacturers that are supplying valsartan for medicinal products authorised in the EU.

NDMA is a genotoxic and carcinogen agent in animals and it is classified as a probable human carcinogen by IARC (International Agency for Research on Cancer, WHO).
Zhejiang Huahai Pharmaceutical provided an initial investigation report on the root cause of the presence of NDMA upon request from the supervisory authority in Italy (AIFA). This initial investigation report by the manufacturer indicates that NDMA formed at a specific step in the valsartan API manufacturing process, and the level of NDMA present may depend on the reaction conditions used.

According to tests of a small random selection of API batches performed by this manufacturer, the levels of NDMA detected range between 3.4 ppm to 120 ppm, with an average of 66.5 ppm. According to the principles of ICH-M7, these levels raise concerns.

In view of the above, it is therefore necessary to evaluate for the medicinal products containing valsartan manufactured by Zhejiang Huahai Pharmaceutical at the site in Chuannan:

- the levels of the NDMA impurity and the reaction conditions used in the manufacturing process,
- the potential risks and any appropriate risk minimisation measures for patients that have been exposed.
- the suitability of the manufacturing process including the reason for the presence of NDMA in the active substance, the suitability of the in-process controls, the analytical methods used and the specifications of the active substance and finished product.

As some of the other valsartan APIs manufacturers may use the same or similar manufacturing process that would therefore potentially generate NDMA, all valsartan containing medicinal products would need to be considered as part of this review.

The issues related to the valsartan manufacturing processes might also be relevant for other APIs and would need to be considered as appropriate.

In view of the above and the necessity to conduct an EU assessment for any potential action to be taken at EU level, the European Commission considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC on the issues raised above and its impact on public health as soon as possible and to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked at the latest by 31 December 2018.

Signed [redacted] Date 5.07.2018