EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring
Head of Unit

Brussels,
SANTE/B5/HL/an(2018)ddg1.b5.5415218

By email only

To the European Medicines Agency,

Subject: Referral under Article 31 of Directive 2001/83/EC – Valsartan-containing medicinal products

We refer to the letter of the European Medicines Agency dated 20 September 2018 concerning the referral procedure under Article 31 of Directive 2001/83/EC concerning valsartan-containing medicinal products, which was initiated by the Commission by notification of 5 July 2018.

With this notification the Commission asked the Agency to consider whether issues that have been identified for the valsartan manufacturing process would also be relevant for other active pharmaceutical ingredients. You explained in your letter that the potential contamination of other sartans by N-nitrosamines impurities was investigated. According to your assessment there is contamination of other sartans and it is considered appropriate to include all the sartans that contain a tetrazole ring in this referral procedure. You therefore recommend to extend the scope of this procedure.

We concur with this approach and confirm that the extended scope of this referral should be as follows:

Product Name(s) in the Referring Member State, if applicable	See Annex I
Active substance(s)	Valsartan, Losartan, Olmesartan, Irbesartan, Candesartan

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

The European Commission considers that it is in the interest of the Union to assess the necessity for any potential action to be taken at EU level for all products referred to above.

As stated in the initial notification, the Commission requests that the CHMP gives its opinion under Article 31 of Directive 2001/83, including on whether marketing authorisations of these products should be maintained, varied, suspended, or revoked, as soon as possible and at the latest by 31 December 2018.

Yours sincerely,

[Electronically signed]

Olga Solomon

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2018
EMA/640541/2018
Human Medicines Evaluation Division

Ms Olga Solomon
European Commission
DG SANTE
B5 – Medicines: policy, authorisation and monitoring
Rue Belliard 232
1040 Brussels
Belgium

Ref.: Referral under Article 31 of directive 2001/83/EC on the presence of N-Nitrosamines in some valsartan-containing medicinal products – extension of scope

Dear Ms Solomon,

We are contacting the European Commission services concerning the ongoing referral under Article 31 of Directive 2001/83/EC for valsartan containing medicinal products initiated following the detection of NDMA impurity in some batches of valsartan products. As part of the testing strategy implemented by OMCLs to investigate potential contamination of other sartans by N-nitrosamines impurities, the EU authorities were notified on the 14th September 2018 that the Bavarian OMCL has detected trace amounts of N-Nitrosodiethylamine (NDEA) in one batch of the active substance losartan manufactured by Hetero Labs Limited (India) and in finished products made from this batch.

Whilst the root cause of the presence of certain *N*-nitrosamines in some batches of valsartan and losartan is currently under investigation, there are sufficient reasons to believe that the quenching of azides used to synthesize the tetrazole ring with sodium nitrite in an acidic environment could lead to the generation of *N*-nitrosamines of secondary amines. Secondary amines could be present deliberately or be contaminants in or degradation products of reagents and/or solvents used in the process. Therefore, it is considered appropriate to further investigate the potential risk of generation of *N*-nitrosamine impurities in the manufacturing process of all the sartans that contain a tetrazole ring.

In light of the above and the new information received on the presence of NDEA in losartan, the European Medicines Agency considers it appropriate that the assessment conducted by the CHMP for valsartan containing medicinal products within the Article 31 referral procedure is extended to all sartans that contain a tetrazole ring (please also refer to the below table). It bears noting that this is raised from the activities of investigation of impurities conducted for all sartans and is in line with the request from the EC to consider any impact on the referral scope and any appropriate actions for other sartans as needed.

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Product Name(s) in the Referring Member State, if applicable	See Annex I
Active substance(s)	Valsartan, Losartan, Olmesartan, Irbesartan, Candesartan
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

Yours Sincerely,

[redacted]

Zaide Frias

Head of Human Medicines Evaluation Division