Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

September 2021
CMDh/433/2021

Subject: Azido impurity in losartan confirmed positive in bacterial mutagenicity test – action needed

Dear Marketing Authorisation Holder,

In April 2021 CMDh has published a letter to MAHs about the risk of a mutagenic azido impurity in sartan containing medicinal products (CMDh/430/2021, impurity 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole, CAS 152708-24-2) ("azido tetrazole impurity"). MAHs of sartan containing medicinal products were requested to conduct an investigation about the risk of contamination of their sartan-containing medicinal product with the before mentioned or related azido-compounds above the TTC.

Recently information has been received about the presence of a second azido impurity in batches of losartan potassium: 5-[4' -[(5-(Azidomethyl)-2-butyl-4-chloro-1 H-imidazol-1-yl)methyl]-[1,1'-biphenyl]2-yl]-1H-tetrazole (CAS 727718-93-6) ("losartan azido impurity"), which has tested positive in a bacterial mutagenicity (Ames) test. This impurity is a losartan related impurity, other sartan products are not impacted by the formation of this impurity.

In the absence of additional information from in vivo studies it is necessary to ensure that 5-[4' -[(5-(Azidomethyl)-2-butyl-4-chloro-1 H-imidazol-1-yl)methyl]-[1,1'-biphenyl]-2-yl]-1H-tetrazole is controlled at or below the Threshold of Toxicological Concern (TTC) as outlined in ICH M7 for known mutagens with unknown carcinogenic potential (class 2) via a suitable control strategy.

Therefore, we ask you to review if there is a risk of contamination of your losartan-containing medicinal product with the before mentioned azido-compound above the TTC. For example, if at any stage of the process an azide is used as a reagent, this should be seen as a risk. Confirmatory tests should be conducted if a possible risk has been identified. In case the product contains also other mutagenic impurities (including nitrosamines) this should be taken into account in the risk assessment. We note that in parallel, EDQM is contacting holders of CEPs.

In line with the considerations for marketed products outlined in ICH M7, if you identify a risk of contamination that has so far not been considered or is so far not appropriately controlled, you are required to take action to ensure that the level of these impurities is below the TTC and to put in place an appropriate control strategy. This may require a variation to the marketing authorisation.

Submission of response:

- Your response should be sent via e-mail to all national competent authorities where the respective product is authorised (for contact points see Annex below). Also, in case no risk has been identified this should be reported.
- Responses should be submitted as soon as the individual risk assessment is finalised, but no later than 2 months from publication of the CMDh letter.
- The heading of the e-mail should include "Outcome of risk assessment - Azido impurity in losartan". For MRP/DCP products the EU procedure number should be added as well.
- For MRP/DCP products the RMS will perform the assessment on behalf of the CMS(s). If the risk assessment has been submitted for a purely national marketing authorisation, please indicate in your response if the product is authorised in other member states and the same data package applies. Please then provide the list of affected MS and authorisation numbers. A preferred lead Member state may also be proposed.
- If confirmatory testing reveals that batches currently on the market in the EEA exceed the applicable TTC limit a Quality Defect should be reported in parallel to the e-mail notification mentioned above to the relevant competent authority as soon as possible as set out in Article 13 of Directive 2003/94/EC.

Please contact the national competent authority (in case of a purely national marketing authorisation) or RMS (in case of an MRP/DCP product) if you have any questions.

Sincerely,

Annex: Contact points for submission of risk assessment

Member State	**Email address**
Austria	nat@basg.gv.at
Belgium	postlicensing@fagg-afmps.be
Bulgaria	nitrosamines@bda.bg
Croatia	nitrosamines@halmed.hr
Cyprus	cy-regulatory@phs.moh.gov.cy
Czech Republic	impurity@sukl.cz
Denmark	godkendelse@dkma.dk
Estonia	nitrosamines@ravimiamet.ee
Finland	mrp@fimea.fi
France	dvs.defauts-qualite@ansm.sante.fr
Germany	12.3@bfarm.de
Greece	nitrosamines@eof.gr
Hungary	mrp-dcp-new-rms@ogyei.gov.hu
Iceland	ima@ima.is
Ireland	regaffairs@hpra.ie
Italy	azidoimpurity_losartan@aifa.gov.it
Latvia	nitrosamines@zva.gov.lv
Lithuania	vvkt@vvkt.lt
Luxembourg	QualityDefects@ms.etat.lu
Malta	mrp-dcp.adm@gov.mt
Norway	nitrosamines@legemiddelverket.no
Poland	sartans@urpl.gov.pl
Portugal	PT_CHMP_Referrals@infarmed.pt
Romania	impuritati@anm.ro
Slovakia	nitrosamines@sukl.sk
Slovenia	nitrosamines@jazmp.si
Spain	dquimica@aemps.es
Sweden	RIC@mpa.se
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