



April 2021
CMDh/430/2021

Subject: Azido impurity in irbesartan confirmed positive in bacterial mutagenicity test – action needed if there is a risk of the presence of azido-impurities above the Threshold of Toxicological Concern (TTC)

Dear Marketing Authorisation Holder,

We are writing to you as you hold a marketing authorisation for a sartan-containing medicinal product to inform you that the impurity 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1*H*-tetrazole (CAS number 152708-24-2) has tested positive in two independent bacterial mutagenicity (Ames) tests.

In the absence of additional information from *in vivo* studies it is necessary to ensure that 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1*H*-tetrazole and related azido compounds are 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 sartan-containing medicinal product with the before mentioned or related azido-compounds above the TTC. We note that in parallel, EDQM is contacting holders of CEPs for relevant sartans. If at any stage of the process an azide is used as a reagent, this should be seen as a risk.

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.

If confirmatory testing reveals that batches of medicinal product currently on the market in the EEA exceed the applicable TTC limit, regulatory action may be needed, and the **Quality Defect should be reported** to the relevant competent authority **as soon as possible** as set out in Article 13 of Directive 2003/94/EC.

For nationally authorised products, please contact the national competent authority, if you have any questions.

Sincerely,