Nur zur Information

für pharmazeutische Unternehmer von Hydrochlorothiazid-haltigen Mono-Arzneimitteln und Hydrochlorothiazid-haltigen Kombinations-Arzneimitteln außer der Kombiniation "Hydrochlorothiazid / Spironolacton" mit der Bitte um eigenverantwortliche Überprüfung der Fach- und Gebrauchsinformationen ihrer Arzneimittel und ggf. um entsprechende Anpassung/en im Rahmen einer/von geeigneten separaten Variation/s.
Hinweis: Rein vorsorglich weisen wir darauf hin, dass hierzu eine Variation vom Typ IAIN nicht akzeptabel ist (s. Erläuterung im Bescheid).

Anlage 4

Zu Hydrochlorothiazid vom BfArM gelb hervorgehoben (Seite 2 + 3)

For information only

for MAH of hydrochlorothiazide-containing mono-medicinal products and hydrochlorothiazide-containing combination products other than the combination "hydrochlorothiazide / spironolacton". We kindly ask these MAHs to check the product information of their medicinal products on their own responsibility and, if necessary - to update accordingly in suitable separate variation procedure(s). Note: As a purely precautionary measure, we would like to point out, that a type IAIN variation is not acceptable (see explanation in the notification of BfArM).

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

23 September 2021
EMA/CMDh/486195/2021

Report from the CMDh meeting held on 14-16 September 2021

Risk of azido-impurity in losartan-containing medicinal products

Following the publication of a letter to MAHs of sartan-containing medicinal products to inform them about the possible presence of the impurity 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole (CAS number 152708-24-2) in April 2021, a second azido impurity has been identified 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)), which has also 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 line with the publication in April, the CMDh agreed to publish a letter addressed to MAHs of losartan-containing medicinal products to ask them to review if there is a risk of contamination of their losartan-containing medicinal product with the before mentioned azido-compound and to ensure that the impurity 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. MAHs of losartan containing products are requested to perform the necessary risk assessment within 2 months and to send the results to the relevant national authorities.

In line with the considerations for marketed products outlined in ICH M7, if MAHs identify a risk of contamination that has so far not been considered or is so far not appropriately controlled, they 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.

Further information on the risk assessment and the submission of responses to the request is included in the letter, which will be published on the CMDh website under “Advice from CMDh”.

Reminder to MAHs for products containing chlorobutanol as an excipient at a level above the permitted daily exposure limit

Following discussions at CMDh in February 2021 (agenda item 3.6), NCAs have sent letters to MAHs for products containing chlorobutanol as an excipient at a level above the permitted daily exposure limit

(PDE) established by SWP, including also products for short term or local use. The MAHs of each product exceeding the permitted daily exposure for chlorobutanol are expected to provide a justification for the acceptability of the level present in their product, and to reformulate products as necessary. These risk assessments were due by 1 September 2021, therefore MAHs are reminded to submit these now as a matter of urgency, if they have not already done so. The risk assessment should be submitted as a type II variation (C.I.13). MAHs are strongly advised to use the variation worksharing procedure whenever possible.

CMDh positions following PSUSA procedures for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendations and the PRAC assessment reports, agreed by consensus on the variations of the marketing authorisations of medicinal products containing the following active substances:

- 5-fluorouracil (i.v. application)
- allopurinol
- amiodarone
- amitriptyline / perphenazine
- amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide
- betamethasone
- carbamazepine
- cefoperazone
- hydrochlorothiazide / spironolactone

The CMDh also agreed an update of the CMDh position for the PSUSA procedure of octreotide (PSUSA 00002201/202006), following an update of the corresponding PRAC recommendation. The initial CMDh position was adopted in February 2021. In the update it is clarified that the outcome of the PSUSA is only applicable to medicinal products containing octreotide for intravenous administration. MAHs that have implemented the PSUSA outcome in the product information of medicinal products containing octreotide authorised for other methods of administration than for intravenous use should update their product information by removing the implemented wording as an editorial change with the next regulatory activity affecting the product information.

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

Products containing hydrochlorothiazide as mono-component or in fixed dose combinations

In the framework of the PSUSA on hydrochlorothiazide / spironolactone, the PRAC noted that hydrochlorothiazide (HCTZ) is also authorised as a single agent and in other fixed dose combination products. The PRAC considers that the risk of acute respiratory distress syndrome (ARDS) would also be relevant to be included in products containing HCTZ as a single agent or as fixed dose combinations of HCTZ considering the following:

- ARDS was established in relation to HCTZ and serious cases of ARDS in relation to HCTZ use have been reported, in which HCTZ was unrecognised as cause of ARDS, leading to re-exposure and life-threatening reactions;
- Raising awareness of healthcare professionals to recognise HCTZ as a potential cause of acute respiratory toxicity is crucial in preventing re-exposure leading to a recurrence of life-threatening reactions.

The wording applies to all hydrochlorothiazide containing medicinal products, as causal relationship of this ADR was established in relation to HCTZ use. If there is a reference to respiratory toxicity, pneumonitis, ARDS or pulmonary oedema already included in the SmPC sections 4.4 and 4.8, the proposed recommendations should complement current wording in place and conflicting wording should be removed. The same applies for the package leaflet.

The same timelines for implementation as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

Products containing rosuvastatin (as mono-component or in fixed dose combination)

In March 2021, following the finalisation of the PSUSA on ezetimibe / rosuvastatin, the CMDh published a request to MAHs of products containing rosuvastatin (as mono-component or in fixed dose combination) to include the interaction with ticagrelor in their product information. In May 2021, the CMDh informed concerned MAHs that the implementation should be put on hold until a further assessment of the interaction during the PSUSA on ticagrelor is finalised. The PRAC has now finalised this assessment and the final agreed wording has been adopted by CHMP. MAHs of products containing rosuvastatin (as mono-component or in fixed dose combination) are requested to include the interaction with ticagrelor in their product information according to the outcome of the PSUSA on ticagrelor. The same timelines as for the present PSUSA for ticagrelor would apply in accordance with the CMDh guidance on implementing variations. MAHs that have already implemented the previous recommendation should update their product information by submitting an editorial change with the next regulatory activity affecting the product information.

Products containing amitriptyline (in fixed dose combination)

In the framework of the PSUSA on amitriptyline, amitriptyline / amitriptylinoxide, amitriptylinoxide, the PRAC noted that amitriptyline is also authorised in fixed dose combination products. The PRAC considered that the additional signs and symptoms of paediatric intoxication, interaction with duloxetine and Brugada syndrome, recommended to be included in the Product Information, could be extrapolated for fixed dose combinations containing amitriptyline, as the amitriptyline component of these products is expected to produce similar adverse reactions due to the similarities in the populations treated.

The same timelines as for the present PSUSA would apply in accordance with the CMDh guidance on implementing variations.

Outcomes of informal PSUR work-sharing procedures

The CMDh has adopted the conclusions of the PSUR assessment for:

- Droslind/Nusvelta/Slenma/Slinda/Stelista (drospirenone)