Annex I

Scientific conclusions

Scientific conclusions

As part of the assessment of the Art. 31 referral procedure for sartans with a tetrazole ring, the Committee recommended that the conditions for sartans with a tetrazole ring should be reviewed to take into account the recommendations from the Art. 5(3) on nitrosamines. On 29 July 2020 the EC sent a letter to EMA requesting the assessment of the impact of the outcome of the Article 5(3) assessment on nitrosamines adopted on 25 June 2020 on the CHMPs opinion of 31 January 2019 for the scientific assessment and review under Article 31 of Directive 2001/83/EC regarding angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471).

Overall summary of the scientific evaluation

Based on the knowledge acquired on the presence of nitrosamines in medicinal products since the sartans referral and taking into account the data assessed within the Art. 5(3) review, in particular related to the methodology to calculate the limits in case of (poly)contamination and potential root causes, the CHMP considered that the outcome of the sartans referral should be amended to take into account the outcome of the Art. 5(3) review. Having considered that the sartan case is very well studied and the API processes were identified as the main and often only root-cause, the CHMP is of the view that there is no specific aspect that would warrant a general exception for sartans with a tetrazole ring.

In the Art. 5(3) review, the CHMP did not support the approach to control nitrosamines based on analytical capability (i.e., technical limit applied at active pharmaceutical ingredient level), as this does not take into account toxicological data, and limits may be different for different nitrosamines, furthermore it could lead to different actual exposures depending on the daily dose of the medicinal product. Nitrosamines should also be controlled usually at the level of the finished product, as several root causes emerged that are related to finished product manufacturing. The control point for nitrosamines should be selected in such a way that it will give assurance of presence of the impurity below the acceptable limit in the finished product.

The CHMP therefore considers that the recommendations adopted in the Art 5(3) review are also relevant to sartans with tetrazole ring.

In view of the above, the CHMP concluded that the benefit-risk balance of angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan) is favourable subject to changes to the conditions to the Marketing Authorisations as described above.

Grounds for CHMP opinion

Whereas

- The CHMP considered the letter from EC to EMA dated 29 July 2020
- The CHMP reviewed the conditions from the procedure under Article 31 of Directive 2001/83/EC for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan) in the frame of the recommendations from the review under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products
- The CHMP considered that there is no specific aspect that would warrant a general exception for sartans with a tetrazole ring, and agreed moving the NDMA and NDEA specifications from

the active substance to the finished product, with a limit according to ICH M7(R1) principles for cohort of concern substances for lifelong exposure.

- In addition, the Art 5(3) recommendations on multiple nitrosamine contaminations, omission of testing and the option of skip testing are also applicable.
- In general, the risk assessment for finished products sartans with a tetrazole ring can follow the timelines of the call for review for products containing chemically manufactured active substances, considering the effort needed to fully elucidate any potential risks and carry out testing, e.g. for other nitrosamines. The deadline for providing risk assessment for the active substance can however be maintained as two years following initial Commission Decision, as it can be expected that MAHs have already progressed fulfilling this condition.

CHMP opinion

The CHMP, as a consequence, considers that the benefit-risk balance of angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan) remains favourable subject to the amendments to the conditions described above.

Therefore, the CHMP recommends the variation to the terms of the marketing authorisations for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan)

Annex II

Amendments to the conditions to the marketing authorisation(s)

Conditions to the MA	Due date
The MAH must ensure that the manufacturing processes of the active substances used for their finished products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products (Article 5(3) procedure).	17 April 2021
The MAH must ensure that the manufacturing processes of the finished product is reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products.	26 September 2022
For all N-nitrosamines, the MAH must ensure a control strategy is in place for active substance batches used for their finished products.	17 April 2019 (last date of the Commission decisions related to the Article 31 referral adopted in 2019[1])
For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications: Limits for NDMA (96 ng/day) and NDEA (26.5 ng/day) should be implemented for the finished product. The limit should be calculated by dividing the respective limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC. The limit will usually need to be included in the finished product specification. Omission from the specification is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood. Skip testing is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 30% of the limits defined above and the root cause is identified and well-understood. In accordance with the recommendations adopted on N-nitrosamines impurities in human medicinal products (Article 5(3) procedure), where the co-presence of the above N-nitrosamines has been identified in the same finished product, it must be ensured that the cumulative risk of these N-nitrosamines does not exceed a lifetime cancer risk (lifelong exposure) of 1:100,000. An alternative approach where the sum of these two N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified (NDEA) may also	30 June 2021

[1] Commission Implementing Decision C(2019)3157 (final) of 17.4.2019 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisation granted by Decision C(2016)1906(final) for "Amlodipine/Valsartan Mylan - amlodipine/valsartan", medicinal product for human use

be used. The approach chosen for a particular case needs to be duly justified by the MAH. The MAH shall ensure that the control strategy for all N-nitrosamines is updated accordingly.	