Annex I

Scientific conclusions

Scientific conclusions

Sartan-containing medicinal products are important treatment options of serious or potentially serious conditions such as hypertension or certain heart or kidney diseases. Efficacy and safety of sartan-containing medicines in these indications are *per se* well-established and are not questioned in this referral. The key issue of this referral concerns the detection of *N*-nitrosamine (esp. NDMA and/or NDEA) contaminations in sartans, the resulting potential long-term risk to patients and measures to minimise as much as possible these contaminations.

Nitrosamines are chemically simple molecules and can be formed in pharmaceutical manufacturing steps whenever there is a presence of a secondary (or tertiary) amines and nitrites, usually in acidic conditions. This is the background to the current referral procedure. However, it should be noted that nitrosamines can also be formed in many other situations, including in biological processes.

NDMA and NDEA are two of the most potent mutagenic carcinogens known. As soon as the problem of nitrosamine-contamination became known, immediate, precautionary measures were taken by competent authorities across the EU such as recalls of affected batches from pharmacies. Initially, this was only necessary for valsartan containing APIs from few manufacturers but later also for some other sartans with a tetrazole ring.

Assessment of the excess risk of cancer

The impact of NDMA and NDEA on human health is currently only extrapolated from animal studies. However, as the DNA damage mechanisms documented in these studies are also relevant in humans and *in vitro* data in human cells are not significantly different from those in animal cells, it is prudent to assume that effects seen in animals may also occur in humans after exposure to sufficiently large amounts of these nitrosamines.

In addition to NDMA and NDEA, other *N*-nitrosamines have been detected in a few sartan-containing medicinal products. Risks resulting from multiple exposures are considered to add up in patients as mutagenic carcinogens are currently considered as summation toxins.

The ICH M7(R1) guideline sets out principles for determining limits for mutagenic / DNA-reactive impurities. The determination of an acceptable intake (AI) is based on extrapolation of carcinogenic risk from rodent carcinogenicity data, as the dose resulting in one cancer case among 100,000 individuals exposed for a life-time to the impurity. *N*-nitrosamines belong to a “cohort of concern” compounds in this guideline. For these reasons, *N*-nitrosamine impurities in pharmaceuticals such as sartans intended for long-term use should be reduced as much as possible.

A full risk assessment for patients previously exposed to NDMA and/or NDEA impurities in sartans, especially valsartan which was found to contain the highest nitrosamine contamination, is not possible as the real extent of exposure of patients is unknown. For an individual risk assessment, data on the exact drug products and batches used by each individual patient would be necessary. Thus, the risk assessment is based on a potential worst case scenario, which would be a partially combined exposure to the highest levels of NDEA for 4 years (2011 – 2015) and to NDMA for 6 years (2012 – 2018) reported from a sartan, resulting in a cumulative theoretical excess cancer risk of 29.5:100,000 or 1:3390 (0.029%) when extrapolated from the available rat studies according to ICH M7(R1). Compared to the lifetime cancer risk in the European population of approximately 50%, this additional risk is considered to be very low.

Considerations on monitoring of exposed patients

The above stated very small theoretical risk has to be balanced against the risks of potential measures to monitor patients such as colonoscopy or gastroscopy which may exceed the theoretical excess cancer risk. For example, a recent review has estimated risks of perforation of 4 per 10,000 (95% confidence interval, 2-5) and major haemorrhage of 8 per 10,000 (95% confidence interval, 5-14) with screening colonoscopy. In addition, advancing age, comorbidity and use of anticoagulants were found to be strongly associated with both gastrointestinal and non-gastrointestinal complications. Furthermore, the target organ(s) of NDMA/NDEA toxicity in humans are still not sufficiently clear.

For these reasons, CHMP could not identify cancer screening methods that patients would benefit from.

Measures to mitigate the risk

Appropriate regulatory actions (such as quarantine or batch recalls) have been taken where relevant. Additional measures are needed to minimise prospectively the reoccurrence of such contamination.

Based on all available data, the CHMP requires the following:

1. Obligatory risk assessments to be performed for manufacturing processes of the drug substances in order to evaluate the theoretical risk of *N*-nitrosamine formation and contamination

2. Modifying manufacturing processes, where necessary, to minimise contamination as much as possible.

3. Implement a control strategy to detect and control *N*-nitrosamine impurities in the API (or intermediate, if justified).

Specifically, CHMP considered that NDMA and NDEA limits should be as low as technically possible. In this regard, a limit of quantification of 0.03 ppm for NDMA and NDEA would be achievable according to the available data on analytical methods. This limit is considered a sufficiently robust threshold for APIs that can technically be reached. In comparison to the daily intake levels calculated based on ICH M7(R1) using non-clinical toxicology, it is possible to generate additional safety factors ranging from 2.73 – 27.3 for NDMA and 10.0 – 100 for NDEA, by defining 0.03 ppm as the common technical target limit for NDEA and NDMA in tetrazole sartan APIs. The underlying concept of the proposed approach is to keep the amount of *N*-nitrosamine impurities as low as possible, irrespective of the type of sartan or dose.

The limit of 0.03 ppm for NDMA and NDEA will be enforceable after a transitional period of 2 years from the notification of the Commission Decision. During this time period, MAHs and manufacturers are requested to introduce relevant changes to the manufacturing processes of the drug substances, as well as develop appropriate analytical methods while ensuring adequate supply of the market for these essential medicinal products. An interim limit based on daily intakes according to principles in ICH M7(R1) using toxicology data are set in order to control these impurities in the meantime at an acceptable level. These interim limits are based on the maximum daily dose authorised in the EU for each of the sartans and therefore vary between them, as outlined in the table below:

Drug substance	Max. daily dose (mg)	NDEA Limit in ppm in API	NDMA Limit in ppm in API
Valsartan	320	0.082	0.300
Losartan	150	0.177	0.640
Olmesartan	40	0.663	2.400
Irbesartan	300	0.088	0.320
Candesartan	32	0.820	3.000

Should NDMA and NDEA be detected in parallel in an API batch, this should lead to rejection of the respective batch, considering that a combined contamination would translate into a combined risk, which may be higher than one additional case of cancer in 100.000 individuals.

Whilst the measures are focused on NDMA and NDEA, the principles used in this procedure in terms of toxicology assessment, control strategy and changes to the manufacturing processes for drug substances should be applied by analogy to other nitrosamines.

In case of identification of other nitrosamines, this should be forthwith reported to the competent authorities, together with a toxicology assessment of the impurity, a clinical assessment for the exposed patients, a root cause analysis and a corrective action plan (e.g. changes to the manufacturing process).

Overall, taking into account the available data assessed in this procedure, the benefit risk balance of medicines containing a sartan with a tetrazole ring remains positive subject to the conditions imposed.

Grounds for CHMP opinion

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for products containing sartans with a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan)
- The CHMP reviewed data on quality regarding the manufacturing processes of sartans with a tetrazole group, analytical data including test results and available methods, and toxicological data available for the N-nitrosamines found in some of these products. The CHMP also carried out a risk assessment for patients previously exposed to NDMA and NDEA in sartans and calculated daily intake levels based on the principles of ICH M7(R1) which are associated with an additional lifetime risk of 1 in 100,000 patients.
- Based on the analysis of potential root causes the CHMP considered that all the MAHs should perform risk assessment of the manufacturing processes used for the APIs in their finished products to evaluate the risk of *N*-nitrosamine formation and contamination.
- A two-year transition period) is considered acceptable to change production processes to achieve syntheses in which N-nitrosamines are not formed, to adopt analytical methods for the control strategy and in order to avoid product shortages.
- During this period, NDMA and NDEA impurities in the API should be controlled for a transition period at limits calculated based on the principles of ICH M7(R1) using validated assays
- After the transition period, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented, which reflects the lowest quantifiable level based on capability of the available analytical methods.

- In case of detection of other N-nitrosamines this should be forthwith reported to the competent authorities, together with a toxicology assessment of the impurity, a clinical assessment for the exposed patients, a root cause analysis and a corrective action plan.
- CHMP could not identify cancer screening methods that patients would benefit from, considering the uncertainty of the target organ(s) of NDMA/NDEA toxicity in humans and the risks of measures to monitor patients such as colonoscopy or gastroscopy which may exceed the theoretical excess cancer risk.

CHMP opinion

The CHMP, as a consequence, considers that the benefit-risk balance of products containing candesartan, irbesartan, losartan, olmesartan, valsartan remains favourable subject to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for products containing candesartan, irbesartan, losartan, olmesartan, valsartan.

Annex II

Conditions to the marketing authorisation(s)

<table>
<tr><th>Conditions to the MA</th><th>Due date</th></tr>
<tr><td>The MAH must ensure that the manufacturing processes of the drug substances used for their drug products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible.</td><td>Within 2 years after Commission Decision</td></tr>
<tr><td>For all N-nitrosamines the MAH must ensure a control strategy is in place in drug substance batches used for their drug products.</td><td>At the time of Commission Decision</td></tr>
<tr><td>For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications for the drug substance:

1) Limits for NDMA and NDEA outlined below should be implemented for a transitional period of 2 years:

<table>
<tr><th>Drug substance*</th><th>Max. daily dose (mg)</th><th>NDEA Limit in ng/day</th><th>NDEA Limit in ppm in API</th><th>NDMA Limit in ng/day</th><th>NDMA Limit in ppm in API</th></tr>
<tr><td>Valsartan</td><td>320</td><td>26.5</td><td>0.082</td><td>96.0</td><td>0.300</td></tr>
<tr><td>Losartan</td><td>150</td><td>26.5</td><td>0.177</td><td>96.0</td><td>0.640</td></tr>
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<tr><td>Candesartan</td><td>32</td><td>26.5</td><td>0.820</td><td>96.0</td><td>3.000</td></tr>
</table>

* These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.

2) After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.</td><td>At the time of Commission Decision

Within 2 years after Commission Decision</td></tr>
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