EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15th September 2018
EMA/662979/2018
European Medicines Agency

Angiotensin II receptor blockers and risk of cancer after contamination with N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA)

Feasibility analysis

Protocol

Investigators	Alexandra Pacurariu, Karin Hedenmalm, Jim Slattery, Maria Gonzalez Martinez
Sign off	Xavier Kurz
First date:	1st September 2018
Last update:	15th September 2018

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of Contents

1. Background

In June 2018, a MAH found that valsartan API supplied by Zhejiang Huahai (ZH) was contaminated by N-nitrosodimethylamine (NDMA), which is a "probable human carcinogen" as classified by the International Agency for Research on Cancer (IARC) (Class 2a carcinogen) (1). NDMA is an unexpected process impurity for valsartan. A referral was started to investigate the issue and, as precautionary immediate measure, national authorities across the EU recalled from pharmacies all medicines containing valsartan supplied by ZH. In addition, ZH is no longer authorised to manufacture the valsartan active substance for EU medicines.

In September 2018, a further N-nitroso impurity N-nitrosodiethylamine (NDEA) has been found in earlier valsartan batches manufactured by ZH, and more recently also in a batch of losartan manufactured by Hetero Labs, India. Subsequently, as a precautionary measure, the referral was extended to all sartans authorised in the EU which contain a tetrazole ring: candesartan, irbesartan, losartan, olmesartan and valsartan.

The contamination is thought to have occurred for valsartan manufactured by ZH between 2011-2015 for NDEA and NDMA and between 2016-2018 for NDMA only. (2) For the period 2012-2015 the two contaminations are potentially overlapping.

Based on preclinical toxicology studies, the theoretical excess lifetime cancer risk for valsartan exposure was calculated to be 21.5: 100,000 patients if taking 320 mg/day Valsartan contaminated with 24.1 µg for 6 years.(2) For NDEA, the theoretical excess lifetime cancer risk for valsartan exposure was calculated to be 8:100,000 patients if taking 320 mg/day Valsartan contaminated with 3.7 µg for 4 years.

A potential worst case scenario for valsartan would be an exposure to NDEA for 4 years (2011 – 2015) and NDMA exposure for 6 years (2012 – 2018). The cumulative theoretical excess risk would then be 29.5/100,000.

For the other sartans, the maximum level of contaminants is much lower than for valsartan and in some cases unknown or below detection limit, see Table 1. Therefore a theoretical excess risk per substance will not be calculated, as it is not considered relevant.

Table 1 Maximum level of contaminants per substance

	Maximum level (ppm)	
	NDMA	NDEA
Candesartan	0.272	0.08
Irbesartan	Below detection	Below detection
Losartan	0.092	0.054
Olmesartan	Unlikely to be contaminated	
Valsartan	61.3	11.53

Of note, NMDA might also be present in contaminated food and beverages and in the environment in general.

From the existing preclinical data, it appears that the liver and the gastrointestinal tract might be potential sites for carcinogenic effect, however the target organs for humans are still under investigation by the Safety Working Party (SWP).(8)

2. Objectives

This is a feasibility analysis to inform a potential epidemiological study of an association beween exposure to contaminated sartans products and occurrence of cancer.

The objectives of this feasibility analysis are:

- to estimate the sample size (number of exposed patients) that would be needed to identify an excess risk of cancer associated with sartans under different assumptions about the background rate of cancer in Europe and assumptions of the relative risk.
- to identify European population databases that would be appropriate to analyse this risk and estimate whether their size in terms of estimated exposure to sartans would be adequate for the analysis.
-

3. Methods

3.1. Sartans exposure patterns in Europe

The overall exposure of sartans in Europe will be evaluated from publicly accessible prescription and sales databases in the following countries: Sweden, Norway, Denmark, Finland, Netherlands and France. In addition, the number of patients with a prescription for sartans was collected from two in-house databases, IMS France and IMS Germany.

The consumption will be expressed in number of patients/year and prescriptions/year, depending on how data is recorded.

In order to estimate the adequacy of data sources needed to identify an excess risk of cancer in the available databases, we will estimate the percentage of the population exposed to all sartans and to valsartan (if the analysis is restricted to this substance) in the six countries, using population size reported by Eurostat.

3.2. Power calculations

Baseline risk of cancer

The baseline risk of cancer in a population is difficult to estimate precisely as it varies with ethnicity, gender, race, country and the type of cancer. A range of estimates will be obtained from the peer-reviewed literature, including reports from European Cancer Information System (ECIS). The Referral Assessment Report will be also considered.

As sartans are used by an older population and the survival time is shorter, the cumulative risk of cancer will be lower for sartan treated patients than for the general population.

As there is no clear indication regarding what is the main targert organ for NDMA toxicity, the calculation is performed for a composite outcome of all type of cancers (except melanoma) grouped together.

Assumptions

There are many uncertainties around parameters as relative risk, percentage of contaminated product and duration of exposure to the contaminant. Therefore, the following assumptions are made for the sample size calculation. They may change when additional information becomes available.

- We assume that all the products in Europe are contaminated (100% contamination degree). This is because the list of contaminated products is likely to be different from country to country and there is a lack of information on which brands are contaminated and what is their market share in each country. Any patient exposed during the contamination period is considered likely to have been exposed to a contaminated product.
- The percentage of the total population being exposed to all sartans in the 6 countries for which public data was available is representative of the whole EU population.
- The theoretical excess lifetime cancer risk for valsartan exposure is considered to be 29.5:100,000 (the worst case scenario estimate for taking valsartan contaminated to NDEA for 4 years (2011 – 2015) and NDMA exposure for 6 years (2012 – 2018).
- As the level of contamination for other sartans is much lower than for valsartan, there is no excess risk estimate calculated for other sartans. Therefore, this feasibility analysis is performed for valsartan only.

Sample size needed to detect the estimated relative risk

Considering the upper bound of the estimated excess risk, the background incidence rate of cancer, alpha of 5%, power of 80% we will calculate the Sample size needed to detect the estimated relative risk.

Sample size needed to exclude a minimum excess risk

An alternative sample size analysis could be made by calculating the sample size needed to allow exclusion of a pre-defined risk of cancer with a pre-defined power, eg, the minimum excess rates per 100,000 patients in the exposed group that can be excluded with 95% confidence.

3.3. European databases suitable for study on association between sartans and cancer

Thirty-three (33) European databases were identified from ENCePP's databases repository and from a previous publication.[1] They will be evaluated to see how suitable they are for the investigation of this potential association. The databases' information will obtained from publicly available information. The criteria used for evaluation are:

- Sufficient population capture, both in numbers and follow-up duration

- Sufficient capture of cancer related outcomes and acceptable quality of the recorded outcomes (cancer-related registries are considered gold standard due to the quality of outcome capture)

- Sufficient capture of exposure to sartans and an adequate level of detail regarding the exposure strength, dose, brand name and batch number

- Time window: if the database captures the relevant time window after the start of contamination

[1] Pacurariu A, Plueschke K, McGettigan P, et al Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation BMJ Open 2018;8:e023090. doi: 10.1136/bmjopen-2018-023090

Published studies on cancer conducted within these databases will be identified from Pubmed, to check the real world use of these databases to study cancer associations.

Limitations: as the information was mainly obtained from publicly available sources, there might be some discrepancies with the current functionalities of the database. In order to solve this limitation, pre-selected databases might be individually contacted in order to obtain further information on duration of follow up as well as other particularities (e.g. coding of brand name, linkage to other databases/registries).

4. References

1. International Agency for Research on Cancer, Weltgesundheitsorganisation, editors. IARC monographs on the evaluation of carcinogenic risks to humans, volume 100 B, biological agents: this publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24 February - 03 March 2009. Lyon: IARC; 2012. 475 p.

2. EMA. Reader's guidance, Valsartan referral. 2018 Sep;

3. Pinheiro SP, Rivera DR, Graham DJ, Freedman AN, Major JM, Penberthy L, et al. Challenges in evaluating cancer as a clinical outcome in postapproval studies of drug safety. Ann Epidemiol. 2016 Nov;26(11):735–40.

4. Pottegård A, Friis S, Stürmer T, Hallas J, Bahmanyar S. Considerations for Pharmacoepidemiological Studies of Drug-Cancer Associations. Basic Clin Pharmacol Toxicol. 2018 May;122(5):451–9.

5. European Cancer Information System [Internet]. [cited 2019 Jan 20]. Available from: https://ecis.jrc.ec.europa.eu/explorer.php?$0-0$1-All$2-All$4-1,2$3-0$6-0,14$5-2008,2008$7-7$CEstByCountry$X0_8-3$X0_19-AE28E$X0_20-No$CEstRelative$X1_8-3$X1_9-AE28$X1_19-AE28E$CEstByCountryTable$X2_19-AE28E

6. Age and Cancer Risk: A Potentially Modifiable Relationship - ScienceDirect [Internet]. [cited 2018 Oct 3]. Available from: https://www.sciencedirect.com/science/article/pii/S0749379713006429

7. GmbH A-MDA. Valsartan: ZL findet NDMA in Tabletten [Internet]. Pharmazeutische Zeitung online. [cited 2018 Oct 3]. Available from: https://www.pharmazeutische-zeitung.de/ausgabe-302018/zl-findet-ndma-in-tabletten/

8. The Carcinogenic Potency Project (CPDB) [Internet]. [cited 2018 Oct 3]. Available from: https://toxnet.nlm.nih.gov/cpdb/