Sartan medicines: contamination by impurities which are probable carcinogens

- **Since mid-2018, nitrosamines, which are "probable carcinogens", have been found worldwide as impurities in drugs containing *valsartan*, *losartan* or *irbesartan*. Their presence has resulted in the recall of many batches.**

- **In the European Union, while awaiting improved production safety, five sartan medicines containing a tetrazole ring (*candesartan*, *irbesartan*, *losartan*, *olmesartan* and *valsartan*) will be marketed until 2021 with potentially detectable levels of impurities. It would seem advisable to avoid them.**

- **This alert shows that the system which is intended to guarantee the pharmaceutical quality of drugs has weaknesses and needs to be improved.**

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Sartan medicines are principally authorised for use in hypertension. As of 2 May 2019, seven sartans were marketed in France: *candesartan*, *eprosartan*, *irbesartan*, *losartan*, *olmesartan*, *telmisartan* and *valsartan* (1).

Reports of impurities and recall of batches. Since mid-2018, in the EU, US and Canada in particular, health authorities have recalled batches of some generic medicines containing *valsartan*, *irbesartan* or *losartan* (2-5).

In France, in early 2019, these batch recalls affected 60% to 70% of drugs based on *valsartan* (alone or in combination) and 5% of those based on *irbesartan*. As of 6 May 2019, only drugs containing *valsartan* at a dose of 160 mg were subject to supply problems (2).

These batch recalls resulted from the detection of impurities in drugs containing *valsartan*, *irbesartan* or *losartan*. They consisted of N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA) or N-nitroso-N-methyl-4-aminobutyric acid (NMBA) (2-4).

In late June 2018, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) reported that they had information regarding the presence of NDMA in *valsartan* produced by a Chinese manufacturer, without providing any details of the circumstances surrounding this discovery (3,4). Subsequently, NDMA was also found in *valsartan* produced by another Chinese manufacturer, and NDEA was found in *irbesartan* and *losartan* produced by two manufacturers in India (4).

Impurities which are probable carcinogens. These substances are nitrosamines which are classified by the World Health Organization (WHO) as *"probable human carcinogens"* (2-4). NDMA and NDEA are also mutagens (6).

According to the French Health Products Agency (ANSM) and the EMA, there is no known immediate risk to the health of patients who have taken drugs contaminated by these impurities (2,4). Regarding the risk of cancer, the EMA estimated in early 2019, by extrapolation from animal data, that for every 100 000 patients taking the maximum recommended dose of a proprietary drug based on *valsartan* containing the highest quantity of impurities for 6 years, there was a risk of an additional 22 cases of cancer linked to NDMA and an additional 12 cases linked to NDEA (4). The excess cancer risk associated with the presence of NMBA would seem to be of the same order as that linked to NDMA (3).

However, according to the EMA, *"the target organ(s) of NDMA/NDEA toxicity in humans are still not sufficiently clear".* The EMA could not identify *"cancer screening methods that patients* [exposed to these impurities] *would benefit from"* (6,7).

The question of a possible excess of cancers associated with sartan administration had already been raised in 2010, following the results of a meta-analysis of 9 clinical trials (7,8).

In question: a change in the manufacturing process and lack of good manufacturing practice. Modifications to the manufacturing process for *valsartan* in 2012 at some production sites, in particular a change of solvent, have been put forward as an explanation for the presence of these impurities, which appear to be by-products of the synthesis reactions (2-4,9). The FDA has also suggested *"the reuse of materials, such as solvents"* as a cause (3). Inspections carried out by the EMA and the FDA revealed a lack of "good manufacturing practice", in that these impurities should have been looked for when the manufacturing process was changed (3,4).

According to the EMA and the FDA, these impurities are generated during the chemical synthesis of the tetrazole ring contained in the chemical structure of the three sartans which have been subject to batch recalls. This ring is also found in two other ARBs, *candesartan* and *olmesartan*, but as of 2 May 2019, there have been no recalls affecting batches of these two ARBs, either in the EU or the US (2-4).

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A two-year period, from 2019 to 2021, with levels of impurities considered acceptable by the EMA. In early 2019, by extrapolation from animal data, the EMA defined a threshold for NDMA and NDEA contamination above which sartan medicines could not be marketed in the EU. This threshold, 0.03 ppm (parts per million), corresponded to *"the lowest quantifiable level, based on the performance of available analytical methods"*. However, this measure will only come into effect in April 2021, a delay which has not been justified by the EMA (4,6).

Until then, a transition period has been established during which manufacturers will have to review their manufacturing processes *"in order to achieve syntheses without the formation of N-nitrosamines"*. A temporary limit has been established for each of the 5 sartans affected, *"at an acceptable level"* of impurities according to the EMA, on the basis of toxicology data. These limits are determined in relation to the maximum daily dose authorised for each sartan and hence differ for each of them, varying from 0.082 ppm to 0.820 ppm for NDEA, and from 0.3 ppm to 3.0 ppm for NDMA (6).

The EMA has also mentioned looking for the presence of nitrosamines in other drugs. In late April 2019, it announced that NDMA had been found in some batches of the oral hypoglycaemic drug, *pioglitazone* (Actos®). The level of NDMA was considered to be acceptable by the EMA, which nevertheless contacted the manufacturers of *pioglitazone* to request that they test their product and check their manufacturing process. In addition, the EMA has announced the launch of a programme to be carried out with the EU Commission, the EU Directorate for the Quality of Medicines (EDQM) (which publishes, notably, the EU Pharmacopoeia) and European experts, with the aim of considering the measures that need to be established to prevent impurities in drugs from occurring, and to improve the management of incidents when impurities are detected (4).

In practice Sartans are not first-choice drugs for hypertension, and they have not been shown to offer a significant advantage compared to other hypotensives. *Olmesartan* should be avoided because of the risk of serious chronic enteropathy, which has not been found with the other sartans (1). In short, it would seem advisable to reserve *valsartan* and *losartan* for situations where reference hypotensives have failed or have produced excessive adverse effects, and to avoid the other sartans that contain a tetrazole ring which will continue to be marketed until 2021 despite potentially detectable levels of impurities. For two sartans without a tetrazole ring (*eprosartan* and *telmisartan*), there is no recognized risk of nitrosamine contamination, but they do not have established efficacy in hypertension for cardiovascular prevention, based on clinical criteria (1).

These contaminations are a reminder that the raw materials for medicines are often manufactured in a limited number of production facilities, and then sold to a large number of pharmaceutical companies producing the originator medicine and/or generics. As a result of this concentration, a production problem rapidly leads to shortages. This alert once again highlights the importance of checks carried out by drug regulatory agencies within pharmaceutical companies and manufacturers of raw materials (10). Based on the data made publically available, the mandated recall of batches probably came too late in relation to the presumed date of contamination. Although drugs are, in spite of everything, the best monitored health products, the exposure of patients around the whole world and over a period of several years to impurities which are known to be carcinogenic, and which were present in commonly used medicines, shows that the systems intended to guarantee pharmaceutical quality have weaknesses and need to be improved.

Let us hope that the European programme for the prevention of impurities in drugs, announced by the EMA, will hasten these improvements.

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1- Prescrire Rédaction "Patients hypertendus" + "Inhibiteurs de l'enzyme de conversion (IEC) et antagonistes de l'angiotensine II, alias sartans" Interactions Médicamenteuses Prescrire 2019.

2- ANSM "Questions-réponses - sartans (valsartan, irbésartan) : information sur les rappels de lots" 21 January 2019 + "Rappel d'un lot de Losartan Accord 50 mg, comprimé sécable (…)" 21 March 2019 + "Disponibilité des médicaments à base de valsartan et autres sartans en France" 5 April 2019: 12 pages.

3- FDA "FDA provides updates on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall" 1 March 2019 + "FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan" 1 March 2019 + "Questions and answers: impurities found in certain generic angiotensin II receptor blocker (ARB) products" 15 March 2019 + "FDA alerts patients and healthcare professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA" 29 April 2019: 23 pages.

4- EMA "Notification to the CHMP/EMA secretariat of a referral (…) - valsartan" 5 July 2018 + "Update on review of recalled valsartan medicines: preliminary assessment of possible risk to patients - Press release" 2 August 2018 + "EU inspection finds Zhejiang Huahai site non-compliant for manufacture of valsartan: EMA and national authorities considering impact on other active substances produced at the site" 28 September 2018 + "EU authorities take further action in ongoing review of sartans: Zhejiang Huahai placed under increased supervision; Aurobindo Pharma stopped from supplying irbesartan to the EU" 15 October 2018 + "Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities" 1 February 2019 + "Update on nitrosamine impurities: EMA continues to work to prevent impurities in medicines" 26 April 2019: 29 pages.

5- Health Canada "Pro Doc Limitée voluntarily recalls two lots of irbesartan drugs because of nitrosamine impurity" 14 March 2019: 2 pages.

6- European Commission "Commission implementing decision concerning (…) the marketing authorisations of medicinal products (…) which contain the active substances "candesartan", "irbesartan", "losartan", "olmesartan", "valsartan"" + "Annexes" 2 April 2019: 10 pages.

7- EMA - CHMP "Referral under article 31 (...) Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group - Assessment report" 14 February 2019: 41 pages.

8- Prescrire Rédaction "Sartans: excès de cancers?" *Rev Prescrire* 2010; **30** (323): 672.

9- Agravat K "Nitroso impureties in valsartan: how did we miss them?" *Pharmaceutical online*; 30 October 2018: 7 pages.

10- Prescrire Rédaction "Héparines: contamination, allergies graves et décès" *Rev Prescrire* 2008; **28** (297): 497-498.

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