Report on paracetamol & PCA

Summary

This report was drafted at the request of the Minister for Medical Care and Sport with the aim of investigating whether paracetamol is safe and how this is ensured. The reason for possible concerns in this regard is an article published in the NRC of 9 July 2020 in which the newspaper, based on its own investigation, reports that paracetamol in the Netherlands can contain PCA, which is a possibly carcinogenic substance. This report is a collaborative effort by the Medicines Evaluation Board (MEB) and the Health and Youth Care Inspectorate (IGJ).

In this report, it is described how medicines are produced and how the safety of medicines is evaluated and tested. In the course of the chemical production process of every ingredient of a medicine, very small quantities of other chemical compounds, so-called impurities, can be formed. If the production process of paracetamol starts with chlorobenzene, then PCA (para-chloroaniline or 4-chloroaniline) can be formed. Several production routes can be used for making paracetamol, including routes whereby no PCA is formed. However, other impurities may be formed in these routes. The variety in production routes for the same ingredient expands the number of options for the production of medicines, which in turn can be an advantage in terms of the availability of medicines.

As impurities can always be formed, safety limits apply to all production processes with regard to these possible impurities so that the health related risk for patients is as small as possible. Some impurities are potentially carcinogenic. The safety limits for potentially carcinogenic impurities are determined on a global basis. Within that context, it has been agreed that the probability of developing cancer is defined as being negligible if no more than 1 additional person out of 100,000 persons develops cancer as a result of being exposed on a daily basis to the highest permissible dosage of a medicinal product during their entire lifetime. The limit for PCA in paracetamol has been set at a maximum of 34 µg per day upon ingestion of the maximum daily dosage of paracetamol.

The limits for medicines are determined by the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). For foods, the EFSA (European Food Safety Authority) advises the European Commission regarding the applicable limits. In this report, the differences between these safety limits are motivated and explained: the EFSA and the ICH use different calculation methods and they also use different studies in calculating their own limit. The measured quantity of PCA in the batches of paracetamol investigated by the NRC remained below the ICH limit that applies to medicinal products. In addition, the limits set for foods cannot simply be applied to medicines - an opinion also shared by the ICH and EFSA.

This report also explains how medicines are evaluated and tested before being allowed into the Dutch market. Medicines may be marketed in the Netherlands only if a marketing authorisation has been granted for that purpose. The MEB evaluates and monitors the effectiveness, risks, and quality of medicines and sets conditions for entry into the market. The IGJ supervises and monitors the production, the quality, and the use of medicines. The manufacturer of the medicinal product is responsible for the random testing of samples in order to investigate the quality of the product. The IGJ carries out checks to ensure that manufacturers actually execute these tests and, for example, also requests the results of these random samples.

After being granted marketing authorisation, the adverse reactions reported and risks associated with medicinal products are continually monitored by the MEB and the EMA (European Medicines

Agency). The medicinal product can also be subjected to an independent post-marketing investigation. Within that context, an investigation is carried out to determine whether the medicinal products being marketed comply with the specifications approved with the application for the marketing authorisation. In the Netherlands, this laboratory investigation is carried out at the RIVM (National Institute for Public Health). The RIVM reports to the IGJ concerning the results. The RIVM also participates in the network of Official Medicines Control Laboratories (OMCL), a European network in which random samples of medicinal products are taken and investigated. The OMCL takes samples each year of many hundreds of medicinal products authorised in the Netherlands, and investigates to what degree they comply with the quality requirements of the product. If it is concluded that the quality requirements are not met, the fellow inspectorates warn each other and take action. They may, for example, recall a medicine.

In conclusion, the MEB, the IGJ, and their European fellow authorities greatly value the patient safety of medicinal products. However, the formation of impurities during the production of medicinal products cannot be avoided. By setting strict limits, the health risk is minimised as much as possible and therefore becomes negligible. The strict limits set for PCA in paracetamol have not been exceeded. Paracetamol can therefore be used safely by patients in the Netherlands.