Verzoek wederhoor van Zembla/NRC aan het Europees Geneesmiddelenbureau (EMA) op 26 oktober 2020

Dear X,

At the end of this week, the Dutch national newspaper NRC and the Dutch TV programme Zembla are to publish a news item about the contamination of metformin drugs in the Netherlands. Our own research, conducted by a laboratory in the US, shows that half of the metformin supplied in the Netherlands by five large pharmaceutical companies is free of NDMA. However, the other half does contain this carcinogenic substance. 50 pills from 49 different batches were examined. The analysis was carried out by Valisure. https://www.valisure.com/
In terms of NDMA, pills supplied by the pharmaceutical company Mylan were found to have particularly high concentrations.
With an average daily dose of 2,000 mg (four pills of 500 mg each), the international safety limit of 96 ng NDMA (maximum intake per day) appears to have been exceeded for tablets of two different batch numbers. Patients who take these tablets receive 128 ng and 124 ng NDMA respectively per day. The contaminated batches are traceable to their batch numbers 4640164A (expiry date Dec 21) and 4640192A (expiry date Aug 22).

If we assume a maximum daily dose of 3,000 mg, as Mylan specifies in the package information leaflet, then a total of four batches of Mylan score above the safety limit. In addition to the above batches, these batch numbers are: 4640195A (Sep 22) and 4660378A (Sep 21).

NRC and Zembla hope you will answer our questions as accurately and fully as possible.

Questions:

Was EMA aware of the presence of NDMA in metformin drugs marketed by Mylan in the Netherlands? If so, at what point did you become aware of this?
What has EMA done with that information?
Has Mylan informed you about the contamination in the aforementioned batches (see batch numbers) or other batches? If so, what measures have you taken?
What will EMA do with the information we have now provided you? Will the batches be removed from the market?

The deadline for your answer is 9 a.m. on Wednesday 28 October 2020.

Many thanks in advance.

Reactie EMA op 28 oktober 2020

Dear X

Please find below responses to your questions.

With kind regards,

Was EMA aware of the presence of NDMA in metformin drugs marketed by Mylan in the Netherlands? If so, at what point did you become aware of this?
What has EMA done with that information?

EMA became aware of the presence of NDMA in some metformin-containing medicines in December 2019. At first, trace amounts had been found in batches outside the EU (see our press release here).
EMA and the national competent authorities (NCAs) have then started an investigation into the matter and asked companies in the EU to validate testing methods and provide testing results so that the NCAs can have a complete picture in order to take the most appropriate decision to protect public health. Companies have been submitting their test results over the past months and have been given a deadline of 15 November 2020 to provide their final pending responses.

As we mentioned in previous responses, EU national competent authorities are carefully balancing the need to ensure the availability of these critical medicines for diabetic patients with any potential risks that may be caused by presence of very low levels of nitrosamines in these medicines.

EMA and the NCAs are monitoring the situation carefully and will take further regulatory actions as necessary.
In order to ensure patient safety while the investigation is ongoing, in October 2020 EMA and the NCAs have asked marketing authorisation holders for metformin-containing medicines to test their medicines before releasing them onto the market so that any further batches entering the market will be within the limits established by EMA's Article 5(3) review to limit the presence of nitrosamines in human medicines.
EMA's Executive Director had asked the human medicines committee (CHMP) to provide guidance for avoiding the presence of nitrosamine impurities in human medicines in September 2019 and the Committee finalised the review in July 2020.

The national competent authorities are handling this process for nationally authorised products, such as the metformin-containing medicines for which Mylan is a marketing authorisation holder. EMA is dealing with the centrally authorised products.
Therefore, in order to get information on metformin medicines marketed by Mylan in the Netherlands we would refer you to the Medicines Evaluation Board (MEB). We appreciate you are already in contact with their press team.

Has Mylan informed you about the contamination in the aforementioned batches (see batch numbers) or other batches? If so, what measures have you taken?

As previously stated, metformin products for which Mylan is a marketing authorisation holder are authorised via the national procedure, therefore the company has an obligation to report directly to the MEB.

What will EMA do with the information we have now provided you? Will the batches be removed from the market?

The information you have shared with us complements the batch testing results that are being submitted by companies and the entirety of this information will be reviewed by CHMP and CMD(h) who will decide whether any regulatory action is needed. It is important to note, however, that the relevant NCA is responsible for ensuring any market action is taken should it be deemed necessary (e.g. batch recalls).