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CMDh endorses suspension of methadone oral solutions containing high molecular weight povidone

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[1] has endorsed by consensus the recommendation to suspend the marketing authorisation of methadone oral (by mouth) solutions containing high molecular weight povidone. These products will remain suspended until they have been reformulated. Additionally, the CMDh agreed that methadone tablets that contain low molecular weight povidone should remain on the market with changes to the product information.

Methadone is used in rehabilitation programs to prevent or reduce withdrawal symptoms in patients dependent on opioids such as heroin. Some oral formulations of methadone also contain the additive povidone, which is available in different molecular weights. While these medicines are intended for oral use only, some patients may misuse oral methadone formulations by injecting them into a vein. If a medicine containing high molecular weight povidone (known as K90) is misused in this way, the povidone is not excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.

The safety of oral methadone medicines containing povidone was reviewed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), following reports of serious adverse events in former or current drug abusers in Norway, which led to the suspension of methadone oral solutions containing povidone K90 from the Norwegian market.

The PRAC assessed the available safety data on the risks associated with the misuse by injection of methadone medicines containing povidone from post-marketing reports and the published literature, and a group of experts (which included pathologists and addiction experts) was consulted for advice. The PRAC concluded that risk minimisation measures would be insufficient to mitigate the risks with oral solutions containing high molecular weight povidone, and therefore recommended that these products should be suspended. They will need to be appropriately reformulated before being reintroduced on the European market.

For methadone tablets containing povidone of lower molecular weight (e.g. K25 and K30), the available data showed that this kind of povidone is excreted from the body and does not accumulate inside the cells as high molecular weight povidone does. Therefore, these products will remain on the

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States.

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market and changes will be made to the product information (SmPC and package leaflet) to reinforce the message that tablets are for oral administration only and must not be taken in any other way.

As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented in all EU Member States where these medicines are marketed, according to an agreed timetable.

Information to patients

- Methadone is used to treat drug addiction in patients depending on opioids (such as heroin). Oral methadone medicines are available as solutions or tablets, and should only be taken by mouth.
- Some methadone oral solutions contain an additive, povidone. Povidone is available in different molecular weights. If methadone oral solutions containing high molecular weight povidone (K90) are misused by injection instead of being taken by mouth as they are intended, the povidone accumulates inside vital organs and may cause serious harm, with possible fatal consequences.
- Because of the potential harm that could derive from such a misuse (injection into a vein), methadone solutions containing povidone K90 will be suspended.
- Patients taking methadone oral solutions with povidone K90 as part of their rehabilitation program will be switched to other methadone medicines, which do not pose the same risk of povidone accumulating inside vital organs.
- Methadone tablets containing povidone of lower molecular weight can continue to be used, but patients are reminded that they should only be taken by mouth. The risk of harm is reduced with low molecular weight povidone (e.g. K25 and K30) as this type of povidone is excreted from the body and is not expected to accumulate inside the cells as high molecular weight povidone does.
- Patients who have questions or concerns should consult their doctor or another healthcare professional.

Information to healthcare professionals

- Some oral methadone solutions contain high molecular weight povidone (K90), which can be harmful if injected as it is retained in the body and may cause tissue damage.
- Cases of povidone deposits and serious adverse reactions (e.g. anaemia and pathological fractures) have been reported in intravenous drug abusers. The source of povidone could not be confirmed, but is likely to be methadone oral solution containing high molecular weight povidone following misuse by injection.
- Since no measures could be identified to minimise the potential harm with methadone oral solutions containing high molecular weight povidone, these solutions will be suspended. They will need to be reformulated before being reintroduced on the market.
- While these medicines are suspended, healthcare professionals should switch their patients to alternative methadone products.
- The risk of harm is reduced with low molecular weight povidone since it is expected to be readily excreted and not to accumulate inside cells. Methadone tablets containing low molecular weight povidone remain on the market, but their product information will be amended to reinforce the recommendation that these medicines are for oral administration only and must not be used in any other way.

The above recommendations are based on available safety data on the risks associated with the misuse by injection of methadone medicines containing povidone. The efficacy of methadone in opioid substitution therapy was acknowledged and was not questioned in this review.

More about the medicine

Methadone is a synthetic opioid (a morphine-like substance). Methadone-containing medicines are used to treat drug addiction in patients dependent on opioids (such as heroin); methadone prevents or reduces opiate withdrawal symptoms. Treatment with methadone should be given in the context of a wider rehabilitation program. Methadone is also used in the treatment of severe pain.

Oral methadone medicines are available as solutions or tablets; only oral methadone products containing povidone were concerned by this review. Povidone is used in oral solutions as a suspending and dispersing agent, or as a binding agent for tablets. Different types of povidone are available, which vary in their molecular weight (a measure of the size of the molecule). The povidone contained in oral methadone solutions has a high molecular weight (known as K90), while the povidone used in methadone tablets has a low molecular weight (e.g. K25 and K30).

Methadone medicines containing povidone have been authorised via national procedures in several European countries. Oral solutions have been authorised in Denmark, Finland, Malta, Norway, Sweden and the United Kingdom; oral tablets have been authorised in Denmark, Finland, Hungary, Iceland, Norway, Romania, Spain and Sweden.

More about the procedure

The review of oral methadone medicines containing povidone was initiated on 10 April 2014 under Article 107i of Directive 2001/83/EC, also known as the 'urgent Union procedure'. It followed the decision of NOMA, the Norwegian medicines agency, to suspend the only methadone-containing oral solution that contains high molecular weight povidone present on the national market, on the basis of reports of serious adverse events in former or current drug abusers in Norway.

The review was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendation was sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

Because the CMDh reached an agreement by consensus, it will be implemented by the Member States where the medicines are authorised according to an agreed timetable.

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