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PRAC recommends suspension and reformulation of oral methadone solutions containing high molecular weight povidone

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of oral (by mouth) methadone products containing the additive povidone, and recommends the suspension from the market of oral methadone solutions containing high molecular weight povidone; methadone tablets that contain low molecular weight povidone will 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 solutions by injecting them into a vein. If a medicine containing high molecular weight povidone is misused in this way, the povidone is not easily excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.

The PRAC acknowledged the risk that the target population may misuse oral methadone by injection, and the potential harm deriving from injecting methadone solutions that contain high molecular weight povidone. The PRAC considered that risk minimisation measures would be insufficient to mitigate the risks with these oral solutions, and therefore recommended that these products should be suspended. They will need to be appropriately reformulated before being re-introduced on the European market.

In addition, recommendations have been made to reduce the risk of misuse with methadone tablets containing povidone of lower molecular weight. Low molecular weight povidone is easily excreted from the body and does not accumulate inside the cells as high molecular weight povidone does. For these products, the PRAC recommended changes 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.

To reach its recommendations, the PRAC reviewed available reports of serious adverse events and data from the published literature. It also sought advice from a group of experts, who were asked to comment on the way oral methadone-containing medicines are currently used and on their effectiveness and safety in clinical practice. The experts considered that providing information on the

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risks associated with the misuse of oral methadone products would be of value but would not be sufficient to manage the risk of misuse in patients dependent on opioids, and that high molecular weight povidone should be removed from methadone products.

The PRAC recommendation will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for consideration at its meeting on 21-23 July 2014.

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 at the request of Norway, under Article 107i of Directive 2001/83/EC. It followed reports of serious adverse events in former or current drug abusers in Norway, which led the Norwegian Medicines Agency, NOMA, to suspend the only methadone-containing oral solution that contains povidone present on the national market. NOMA then asked the European Medicines Agency to review the benefit-risk balance of all oral methadone medicines containing povidone in the EU.

The EU-wide review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As oral methadone medicines containing povidone are all authorised nationally, the PRAC recommendation will now be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a regulatory body representing EU Member States, and is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

If the CMDh position is agreed by consensus the agreement will be implemented by the Member States where the medicines are authorised, according to an agreed timetable. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

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