Statens legemiddelverk
Norwegian Medicines Agency

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC E-mail: ReferralNotifications@ema.europa.eu

This notification is an official referral under Article 107i of Directive 2001/83/EC to the PRAC made by Norway – Norwegian Medicines Agency/NOMA

Product Name, Strength and Pharmaceutical Form	Methadone containing medicinal products containing povidone
Marketing Authorisation Holder (MAH) in the referring member state	Martindale Pharmaceuticals Limited Bampton Road, Harold Hill Romford, RM3 8UG Storbritannia

Background

In August 2013, NOMA received 11 ICSRs, all with the suspected drug entered as the excipient polyvinylpyrrolidone (more commonly known as povidone). No trade name of a suspected drug was entered in these reports. The ADRs reported was mainly; kidney failure and drug administered at inappropriate site (see details below). It was clear from the reports that all 11 cases described biopsies from former or current injecting drug abusers (medication error/off-label use/abuse/misuse). Biopsies were taken due to organ failure or autopsy. The biopsies showed macrophages containing material consistent with polyvinylpyrrolidone (=povidone). Literature and staining procedures supports the povidone suspicion. The povidone deposits were found in the kidneys and other tissue.

Povidone is used as an excipient in oral formulations only and is available in a range of molecular sizes. Orally ingested povidone is excreted unchanged. Povidone was previously used in injectables, so it is known that the smaller molecules normally are excreted via the kidneys, while the larger molecules cannot be filtered out, and are known to deposit in tissue.

In a meeting held on the 12th March 2014 NOMA was informed by clinicians and pathologists that they strongly suspected Methadon Martindale as the causal drug in this series of serious adverse reactions (including fatal cases). The background for the suspicion of this particular product was due to the use of povidone K90 (large molecules) as an excipient, and the high amount of povidone 11,7mg/ml. The product is also known to be injected by drug abusers. Other povidone containing products with a potential for abuse in Norway, contain smaller povidone molecules and in smaller amounts.

Methadon Martindale Pharma contains methadone and is authorized in Norway for use as maintenance therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation.

The product is authorized through the Mutual Recognition Procedure with Norway as Reference Member State (NO/H/0151/001). The marketing authorization was renewed in 2011. Concerned Member States are Denmark, Finland, Malta, Sweden and UK.

To reduce the risk for further serious adverse reactions in drug addicts, the NOMA has decided to suspend Methadon Martindale as of 8th April 2014. NOMA has informed the MAH and the public of the withdrawal.

Safety concern – further details

A total of 11 adverse drug reaction reports have been received by NOMA on the 30th August 2013, all from the western part of Norway (Department of Pathology, Haukeland University Hospital, Bergen). The reactions reported were kidney failure in all but one case. In addition to kidney failure, anemia was reported in one case, pain and weight loss was reported in one case and enlarged lymph nodes, stomach pain and weight loss was reported in one case. One fatal case reported both kidney failure and liver disorder. All cases reported product deposit and drug administered at inappropriate site. All the patients were known to be former or current injecting drug abusers. None of the cases reported a suspected medicinal product, but polyvinylpyrrolidone/povidone is reported as the suspected substance.

In contact with the reporters it was clarified that the product deposit found in biopsies from the kidney is "macrophages with bubbles", which is considered to be deposits of povidone. Povidone was identified by staining techniques. The povidone deposits found in the tissue is suggested to originate from liquids that are injected by the patients.

On the 12th March 2014 NOMA was informed of an additional four cases, and on the 18th March of even one additional case. In total 16 cases are now identified from several parts of Norway, three of which are fatal.

The reporters strongly suggest that the suspect drug is Methadon Martindale as this product contains a high amount of povidone K90 (11.7 mg/ml) and has been widely prescribed in the western part of Norway. It is estimated by healthcare providers that about 7 % of patients prescribed methadone in this area are injecting the product instead of the recommended oral administration. Co-administration (by injection) of other povidone containing medicinal products (e.g. Subutex tablets, Suboxone tablets, Buprenorphine tablets, Temgesic tablets and Methadone Abcur tablets) cannot be excluded. However, these products are not suspected to the same degree by the reporters, as the amount of povidone in these products is low(er). The cases are reported to NOMA as medication errors (in drug abusers, i.e. misuse/abuse) leading to serious, even fatal ADRs.

Methadon Martindale is only available through drug rehabilitation programs in Norway.
Legal status: restricted prescription.

Current product information

SmPC section 4.2 Posology:

A criterion for treatment with methadone is that the patient is taking part in a "methadone programme" with drug-assisted rehabilitation for drug abusers, approved by a relevant authority.

For oral administration only. The medicinal product must not be injected.

SmPC section 4.4 Warnings and precautions:

This medicinal product contains sunset yellow (E110), which may cause allergic reactions and orange flavour (including propylene glycol) which may cause alcohol-like symptoms.

There is no information on povidone (are mentioned in list of excipients only).

PIL Section 3. How to use Methadone

You must only take Methadone by mouth. Under no circumstances should you inject this product as injecting it may cause serious and permanent damage to your body with possible fatal consequences.

On outer package: Only for oral use

Additional information

Two other methadone oral solutions are authorized in Norway which does not contain povidone. One of these is marketed for the moment. In Norway there is sufficient stock of the alternative to replace Methadon Martindale. Other methadone products authorized in the EU may however contain povidone and therefore potentially lead to similar safety concerns.

The product (Methadon Martindale) will be suspended from the Norwegian market as of 8th April 2014. The MAH and the pharmacies, relevant authorities and the public were informed of the decision in the evening of the 20th March 2014. The date of the suspension was set to the 8th April to ensure that the pharmacies and drug-assisted-rehabilitation centres have enough time to make alternatives available

Conclusion

Based on information provided by clinicians and ADRs reported to the NOMA, it is considered as a major safety concern that authorised products may cause serious, even fatal reactions, even if due to its incorrect administration. It is considered that the information on correct use of the drug does not prevent the risk, as the drugs are intentionally abused and also known to be distributed on the illegal market. Therefore the NOMA considers that the product should be suspended.

On the basis of the NOMA suspending the medicinal product at issue, the procedure under Article 107i of Directive 2001/83/EC is initiated. The PRAC is requested to give its recommendation as to whether marketing authorisation of methadone products containing povidone should be maintained, varied, suspended, or withdrawn.

Signed

[redacted]

Audun Hågå

General Director

Date

02 April 2014