IN ORDER TO GUARANTEE CONFIDENTIALITY, SOME PARTS OF THE ASSESSMENT REPORT HAVE BEEN DELETED.

Assessment report

Methadon Martindale Pharma

Suspension of marketing authorization in Norway because of risk of serious tissue deposit of povidone when medicines are injected instead of orally administered

Approved in mutual recognition procedure NO/H/0151/001/MR

Disclaimer :

This assessment report was provided by the Norvegian Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the Norvegian Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the Norvegian Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

Name of the products	Methadon Martindale Pharma solution 2mg/ml
Marketing Authorisation Holder(s)	Martindale Pharma

Background

Methadon Martindale Pharma is authorized in mutual recognition procedure NO/H/0151/001/MR for use as maintenance therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation. Other MSs in the procedure: Finland, Sweden, Denmark, Malta and UK.

The product is approved for oral administration. However, it is well known that these products are also injected intravenously by drug abusers in Norway.

The safety problem of concern is reports on permanent deposits of povidone in several vital organs and tissues. 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.

The product suspected to be of particular safety concern is Methadon Martindale Pharma containing povidone K90.

As the suspected product has a known risk of misuse, the following information is currently included in SmPC, PIL and on the outer package:

> *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

Several methadone containing products are marketed in Norway. The most prescribed products are:

- Metadon DnE solution 1 mg/ml, 2 mg/ml and 5 mg/ml (about 68 % of DDDs during 2010-2014) – dose not contain povidone.
- Methadon Martindale Pharma solution 2 mg/ml (about 28 % of DDDs during 2010-2014) – contains povidon.

- Metadon Abcur tablets 5mg and 20 mg (about 0.6 % of DDDs during 2013-2014, marketed Mar 2013) - contains povidone.

Data available

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 and case narratives annexed). 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 povidone. Literature and staining procedures supports the povidone suspicion. The povidone deposits were found in the kidneys and other tissue.

By communications with the reporting pathologists and with clinicians in the drug-assisted rehabilitation program during late autumn 2013, it became more clear that they suspected Methadon Martindale Pharma solution to be the drug most probably associated with the biopsy findings.

A meeting was arranged in Bergen on 12th March with the pathologists who originally reported the cases and clinicians involved in the national drug-assisted rehabilitation program in the region of Western Norway. A nephrologist and a general physician were also present to present relevant clinical cases.

At the meeting, pathologists from <*confidential information deleted*> presented pathology findings from the 11 cases already reported to NOMA and five additional cases with the same type of findings. By applying staining techniques and referencing to similar findings reported in the literature, they concluded that the findings were consistent with generalized pathogenic histiocytoses related to injection of povidone containing products.

The pathologist did not have access to medication history or history of abused medication for the cases. In order to investigate which drug was the most likely candidate for suspicion they had made rough calculations on how much povidone was present in the body, based on the amount of tissue displaced in affected organs. By applying grid analyses in one of the cases, they estimated that around 200 g of povidone would be present in the body in order to cause the changes observed in the biopsies. It cannot be confirmed that drugs supplied in the drug-assisted rehabilitation program are the source of the povidone, but it cannot be excluded. In order to retain as much as 200 g of povidone in the body, the pathologists calculated that one would need to inject buprenorphine 8 mg tablets containing 8 mg povidone K30 (low molecular weight povidone, estimated 50% retention) 50.000 times. For Methadon Martindale solution, which contains 585 mg povidone K90 (high molecular) per 50 ml (considered to be a daily dose within normal dose range), only 342 injections would potentially have the same effect.

To further look into the issues of suspected drugs, a consultant <*confidential information deleted*> presented an overview of the medication used in drug-assisted rehabilitation program in Norway in recent years (2004-2012). Most of the cases in the material from the pathologists are from western part of Norway. Rough estimates of drugs available in the rehabilitation program in the relevant period, indicated the population in Western Norway has indeed been more exposed to povidone than the population in the rest of Norway. The potential exposure from buprenorphine tablets is considerably lower than the exposure from methadone. The only fluid methadone product containing povidone on

the market in Norway is Methadon Martindale Pharma solution 2 mg/ml. This product has been used to a greater extent in the western region than in the rest of the country. According to these considerations, Methadon Martindale Pharma solution is the most likely suspected drug causing the adverse drug reactions reported, if the source of drug supply is considered the drug-assisted rehabilitation program.

To further illuminate the possible effects of povidone accumulation in organs, a physician <*confidential information deleted*> presented a case history. This patient had a long history of extensive intravenous drug abuse, probably also of methadone with povidone. He is now in the drug-assisted rehabilitation program with a high dose of methadone, one morning and one evening dose. The evening dose is given without supervision. Over the last years he has developed increasing gastrointestinal symptoms, anemia and several pathological fractures. Biopsies have revealed extensive povidone-deposits, among others in bone marrow and in the gastrointestinal tract.

Head consultant <*confidential information deleted*>presented two additional case histories from his department. Case number one had apparently injected methadone just a few times (2-3), but had a history of injecting amphetamine. Renal failure was diagnosed and povidone deposits were found in renal biopsies. Currently the renal function is improving. Case number two had a long history of injection of different drugs, among them methadone and Imovane (zopiclone). This case had progressive renal failure.

The pathologists and the clinicians at the meeting were clear that in their view Methadon Martindale Pharma solution prescribed in the drug-assisted rehabilitation program is the most likely legal source of the povidone found in tissue from cases reported. The clinicians responsible for the drug-assisted rehabilitation program asked NOMA to formulate an official information describing the safety concern. This information to be further used as basis for a coordinated information effort towards relevant health care personnel and user organizations. In addition processes should be initiated to investigate the possibilities to remove povidone from drugs with a potential for injection among abused individuals.

Regulatory actions

Three alternative regulatory actions were discussed:

- Information campaign to targeted groups on the safety concern
- Special restriction on the dispensing of the Methadon Martindale Pharma (patients to administer the product orally during supervision of a pharmacist or other health care professional)
- Suspension of the Methadon Martindale Pharma

Following the meeting with pathologists and clinicians from the drug-assisted rehabilitation program by 12th March 2014, NOMA discussed the safety concern with the Norwegian Directorate of Health, (responsible for the drug-assisted rehabilitation program) and the Ministry of Health and Care Services.

Based on these discussions it was 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. Special restriction on the dispensing of the product was discussed, but was considered not to work in daily practice.

NOMA contributes to public health by continuously monitoring the safety of approved medicinal products. Whenever a serious safety concern is identified, it is NOMA's responsibility to take actions to minimize the risk even in situations where medicinal products are known to be used incorrect, if possible. As alternative products without povidone is available on the Norwegian market, it is concluded that the best way to prevent further injury to a vulnerable patient group, as drug abusers are considered to be, will be to suspend Methadon Martindale Pharma.

Methadon Martindale Pharma will be suspended from the Norwegian market as of 8th April 2014. The MAH and the pharmacies, relevant authorities and the public will be informed on the 20th March 2014. The date of the suspension is 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.

Methadon Martindale Pharma 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 is set to the 8th April to ensure that the pharmacies and drug-assisted-rehabilitation centres have enough time to make alternatives available.

Annex

Case summaries

11 serious reports were received by the Norwegian Medicines Agency concerning former or current injecting drug users, age 31 to 53 years old. Reported reactions were “product deposit” and “drug administered at inappropriate site” in addition to failure of various organs. Suspect substance is polyvinylpyrrolidone. Biopsies were taken from these patients due to organ failure or during autopsy. The biopsies have shown macrophages containing material consistent with polyvinylpyrrolidone. The results of the staining were: Periodic acid-silver methenamine (PASM): black, congo red: pink, hematoxylin eosin: grey-blue. Accumulation is suspected due to injection of polyvinylpyrrolidone containing drugs. The causal relationship of the adverse events “drug administered at inappropriate site” and ”product deposit” is assessed as probable. The assessment of the other adverse events will be listed for each individual case summary.

<*confidential information deleted*>: This is a serious report concerning a 44 year old man who is a former drug abuser. Reported adverse event is kidney failure. Concomitant conditions include kidney failure and drug abuse. A kidney biopsy was performed in 2009. The results from the staining were the same as described above. The patient has not recovered from the adverse events. The causal relationship of the adverse reaction kidney failure is assessed as “probable” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 53 year old man who is a drug abuser. Reported adverse event is kidney failure. Concomitant medical conditions include kidney failure and chronic hepatitis C. The patient’s kidney function has been rapidly decreasing for the last 6 months. Creatinine level was 276. Minimal proteinuria has been reported. A kidney biopsy was performed in 2011. The results of the staining were the same as described above. The condition is not recovered/not resolved. The causal relationship of the adverse event is assessed as “possible” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 33 year old man who is a former drug abuser. The reported adverse event is kidney failure. Concomitant medical conditions include kidney failure and hepatitis C. The patient’s creatinine level has been increasing for the last 6 months. No proteinuria has been reported. A kidney biopsy was performed in 2012 due to a suspicion of hepatitis C-related glomerulonephritis. The results from the staining were the same as described above. The patient has not recovered from the adverse event. The causal relationship of the adverse event is assessed as “possible” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 45 year old man who is a drug abuser. The reported adverse events are kidney failure and anemia. Concomitant conditions include kidney failure and anemia. In 2012 the patient developed kidney failure, and a biopsy was performed. In 2013 he developed anemia, and a bone marrow biopsy was performed the same year. The findings were the same in both organs, as described above. The adverse events are not resolved. The Regional Pharmacovigilance Center has assessed the causal relationships of the adverse events. The causal relationship has been assessed as “probable” regarding the anemia as other causes of the bone marrow changes were lacking, and “possible” regarding the kidney failure due to a combination of changes seen in the biopsy.

<*confidential information deleted*>: This is a serious report concerning 36 year old man who is a drug abuser. Concomitant conditions include hepatitis C. The patient underwent biopsy of the bone marrow

in 2012 and of intestinal wall in 2013, for unknown reasons, both with the same results. The results of the staining were the same as described above. The patient has not recovered from the adverse events. The causality is assessed as “probable” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 46 year old female patient. She is a former drug abuser. Reported adverse reaction is kidney failure. The patient’s creatine level has been increasing since the summer of 2012. Concomitant conditions include kidney failure and hypertension for many years, and the hypertension has been treated for 2-3 years. A biopsy was performed in 2013. The results were the same as described above. The patient is not recovered from the event. The causal relationship of the event is assessed as “possible” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 34 year old male patient who was a drug abuser. The reported reactions are death, anemia, liver disorder and kidney failure. Concomitant conditions include drug abuse, weight loss, anemia, pain, kidney failure, bleeding tendency, liver disorder and thrombocytopenia. A bone marrow biopsy was performed in 2011. The results of the staining were the same as described above. The patient died from multi-organ failure 20110222. Autopsy showed massive infiltration of histiocytic cells in bone marrow, lungs, heart, liver, lymph nodes, pancreas, spleen and mesentery/peritoneum. It was concluded that cause of death was bronchial pneumonia and non-Langerhans cell histiocytosis of unknown cause but polyvinylpyrrolidone was suspected. Possible connection to injected tablets was made later. The causal relationship of the events anemia and liver disorder is assessed as “probable” by the Regional Pharmacovigilance Center, based on biopsy findings. Causal relationship of the events death and kidney failure is assessed as “possible” by the Regional Pharmacovigilance Center. The latter is assessed as “possible” because of a lacking confirmation of histiocytosis due to polyvinylpyrrolidone

<*confidential information deleted*>: This is a serious report concerning a 39 year old male who is a drug abuser. Reported reactions are enlarged lymph nodes (since 2012), stomach pain (since 2013), kidney failure and weight loss. Concomitant conditions include hepatitis C, abdominal pain, kidney failure, weight loss and drug abuse. In 2012 a biopsy of the bone marrow was performed, as well as a biopsy of the lymph node. A gastric, duodenal, ileal and colon biopsy was performed in 2013, all with similar results, same as described above. The results of the bone marrow biopsy in 2012 are not included in the report. The patient has not recovered from the events. The causal relationship of the adverse events enlarged lymph nodes, stomach pain and weight loss is assessed as “probable” by the Regional Pharmacovigilance Center. The causal relationship of the event kidney disease is assessed as “possible” because of lacking biopsy confirmation.

<*confidential information deleted*>: This is a serious report concerning a 41 year old male who is a drug abuser. Reported reactions are weight loss, kidney failure and pain. Concomitant conditions include hepatitis C, weight loss, pain, kidney failure, drug abuse and clavicle fracture. In 2012 a biopsy of the clavicle was made due to fracture, the results was reported as osteomyelitis of the clavicle. In 2013 a biopsy of the bone marrow was performed. The biopsies both had similar findings regarding staining, same as described above. The patient has not recovered from the events. The causal relationship of all the reported adverse events is assessed as “possible” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 37 year old male patient. The patient is a drug abuser. The reported adverse event is kidney failure, since 2013. Concomitant conditions include drug abuse and kidney failure. A kidney biopsy was performed in 2013, and the

results were the same as described above. The patient is not recovered from the events. The causal relationship of the events has been assessed as “probable” by the Regional Pharmacovigilance Center.

<*confidential information deleted*>: This is a serious report concerning a 31 year old male patient. The patient is a drug abuser. The reported adverse events are is anemia (sine 2013) and kidney failure. Concomitant conditions include hepatitis C, drug abuse, blood transfusion dependent, anemia and kidney failure. A bone marrow biopsy was performed in 2013, and the results were the same as described above. The patient is not recovered from the events. The causal relationship of the event anemia has been assessed as “probable” by the Regional Pharmacovigilance Center based on the biopsy findings. The causal relationship of the event kidney failure has been assessed as “possible” by the Regional Pharmacovigilance Center as biopsy results are lacking.