# Annex II

# Scientific conclusions

## Scientific conclusions

### Overall summary of the scientific evaluation of methadone products for oral use containing povidone

Methadone is a synthetic opioid. Methadone is used in the treatment of moderate to severe pain and is also used as maintenance/substitution medication in the management of opioid dependence. Treatment with methadone should be given in the context of a wider rehabilitation program, opioid substitution therapy (OST).

On 2nd April 2014, the Norwegian Medicines Agency, NOMA, triggered a referral under Article 107i of Directive 2001/83/EC concerning methadone-containing medicines for oral use containing povidone asking the PRAC to review the benefit-risk balance of all oral methadone medicines containing polyvinylpyrrolidone (more commonly known as povidone or PVP) authorised in the EU and to make a recommendation to the Human Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on any measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn. The review of oral methadone medicines containing povidone started on 10 April 2014 under Article 107i of Directive 2001/83/EC. It followed the decision of NOMA to suspend the only methadone-containing oral solution that contains povidone present on the national market, on the basis of reports of serious adverse events in former or current drug abusers in Norway.

Povidone is an excipient available in a variety of different molecular sizes from K12 (low molecular weight (Mw), average Mw ~ 2000) to K90 (high Mw, average Mw 1,100,000). It is mainly used in oral solutions (K90) as a viscosity-increasing agent, or as a binding agent (e.g. K25, K30) in tablets.

The efficacy of methadone in OST was acknowledged in this referral procedure. The overall effectiveness of methadone maintenance treatment is established in the literature and has been reviewed in several articles. Flexible-dose methadone maintenance therapy is more clinically effective than no drug therapy in dependent opioid users.

***Methadone oral solution containing high molecular weight povidone (K90)***

The PRAC reviewed all available safety data, in particular with regards to the risks associated with the misuse by injection of methadone products for oral use containing povidone. The review took into account 15 cases of serious adverse reactions reported in Norway. The cases concerned former or current injecting drug abusers, aged 24 to 53 years old. Fourteen (14) cases of renal failure were reported. In all cases, staining of biological samples supports the conclusion that povidone accumulated in the affected organs. Six kidney biopsies were presented and all demonstrated deposits of povidone in the tubular-interstitial area. For the other eight cases, renal biopsies were lacking, but povidone deposits were detected in biopsies from other tissues. For five patients, bone destruction and/or bone marrow affection (including anaemia) were reported and findings from biopsies showed accumulation of povidone in the bone marrow. For one of the five patients the bone marrow biopsy showed about 90% histiocytic infiltration characteristic for povidone deposit and only about 5% of bone marrow available for erythropoiesis. Pathological fractures were observed in two of the five patients, with deposits of povidone also in the bone tissue.

The PRAC noted that all these 15 cases reported “intentional drug misuse”, “product deposit” and “drug administered via inappropriate route” and were assessed by the regional pharmacovigilance centre in Norway as possibly or probably related to the injection of povidone. Most of the patients were currently or previously included in OST programs. For 12 of the 15 patients, evidence that they had been prescribed or used methadone (urine sample or patient’s statement) was available. For the other

three patients, this information was lacking. In nine cases a history of drug abuse with substances that have been injected was specified and in eight of these nine cases a history of injecting methadone intended for oral use was reported.

Available data from the scientific literature suggests that an association between deposits of povidone and renal impairment has not been well established. However, the causality of povidone deposits and bone marrow failure and skeletal fracture has been reasonably demonstrated, and the mechanism of pathophysiology appears to be related to the spatial competition of deposits and bone marrow (Kepes et al 1993; Kuo et al 1997; Dunn et al 1998; Huang et al 2012).

The distribution and elimination of povidone when administered intravenously has been well investigated and studies using radioactive labelled povidone of different molecular weight have demonstrated that clearance of polymers after intravenous administration is dependent on molecular weight. Following parenteral administration, it is generally accepted that low molecular weight povidone (Mw <25 000) is readily excreted by the kidney: the glomerulus can excrete within a few days all povidone of Mw 40 000 or below; the normal glomerulus of healthy human subjects is relatively impermeable to povidone Mw >70 000 (while in humans with nephrotic disease, the permeability for larger molecules was increased); the reticuloendothelial system (RES) retains molecules with a Mw >110,000 (Ravin et al. 1952; Hulme and Hardwicke 1968). High molecular weight povidone therefore accumulates if injected intravenously and povidone deposition in organs and tissues (in particular bone marrow and bone tissue) have been reported in the literature after substantial intravenous administration leading to 'povidone storage disease' (Kepes et al. 1993; Kuo et al. 1997; Dunn et al. 1998; Huang et al. 2012).

In the context of the review of methadone products containing povidone, the PRAC noted that high molecular weight povidone was present only in one methadone oral solution dosed at 2 mg/ml (containing high molecular weight povidone, K90). Should this oral solution be repeatedly injected, povidone would be permanently retained and accumulate within organs and tissues, leading to potential serious harm. It was also noted that misuse by injection of methadone product is an inherent risk in the target population with evidence showing an occurrence of injection of methadone for oral use among injecting drug users varying from 5.0% to 79.5% (Winstock et al. 2010, Guichard et al. 2003, Waldvogel et al 2005, Judson G et al. 2010, and Vlahov D et al. 2007) and an underreporting considered to be likely.

Although the brand of methadone cannot be confirmed with certainty it is suspected, based on the availability of the product and pattern of usage in Western Norway that the observed serious adverse reactions (e.g. anaemia and bone marrow disorder) were caused by povidone deposition in drug abusers who have misused methadone oral solutions containing povidone K90.

The inclusion of povidone K90 in oral methadone solutions was initially intended to enhance viscosity and reduce the risk of misuse by injection. However, available data do not demonstrate the effectiveness of povidone in mitigating this risk. The product information of this methadone oral solution already contains clear advice that it should not be injected. Additional warnings in the label were further considered, but a direct information to the patients is challenging and according to the experts, such measures are unlikely to further minimise the risk of injection. Supervised administration of every dose was also discussed but this would be difficult to consistently incorporate into daily OST practice and would lead to serious non-compliance. Therefore, the PRAC considered that additional risk minimisation measures could not mitigate the known risk of misuse by the intended target population and the associated potential serious harm caused by the injection of high molecular weight povidone (K90).

Considering the reported serious adverse reactions, including bone marrow affection (e.g. anaemia) and pathological fractures as well as the potential for accumulation of high Mw povidone when injected,

in addition to the acknowledged difficulty of adequately mitigate the well-known risk of misuse in the target population, the PRAC concluded that the benefits no longer outweigh the risks for methadone oral solution containing povidone K90. Therefore, the PRAC recommends the suspension of this product. To lift the suspension, this product should be appropriately reformulated taking into account its misuse potential.

***Methadone tablets containing low Mw povidone (K25 or K30)***

Other methadone products containing povidone concerned by the review are tablets and have lower Mw povidone (e.g. K25, K30, also in lower amount), which is known to be excreted from the kidney and therefore is expected not to be retained in the body. These products are therefore not associated with the potential for harm of oral solutions containing high Mw.

The PRAC concluded that the benefit-risk of these products was favourable provided that amendments are introduced in the product information, to harmonise and reinforce the message that tablets are for oral administration only and must not be injected.

## Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for methadone medicinal products for oral use containing povidone.
- The PRAC reviewed all available data from published literature, pre-clinical and clinical studies and post-marketing experience on the safety of methadone medicinal products for oral use containing povidone, responses submitted by the marketing authorisation holders (MAHs) in writing and during the oral explanations, the outcome of the ad-hoc expert advisory group meeting as well as stakeholders' submissions in particular with regards to the risks associated with the misuse of the products by injection which is a well-known risk in the target population;
- The PRAC considered case reports, including fatal cases, in former or current injecting drug users, and noted the serious adverse reactions, the nature of which (including bone marrow adverse effects and pathological fractures) was consistent with the accumulation of povidone and also noted that povidone deposition in organs and tissues had been seen on biopsies. In most cases, prescription or use of methadone can be confirmed, while some of them also have admitted injecting oral methadone.
- The PRAC was of the opinion that available pre-clinical and clinical data provide evidence that high molecular weight povidone (>110,000) when injected is likely to be permanently retained in the body, in particular in the bone marrow and bone tissue. This leads to 'povidone storage disease' that may cause serious harm. There is evidence that lower molecular weight povidone (<25,000) is readily excreted but that higher Mw povidone (>110,000) is not, or (>70,000) only partially excreted;

***Methadone oral solution containing high molecular weight povidone (K90)***

- The PRAC noted that high molecular weight povidone was present only in one methadone oral solution dosed at 2 mg/ml, which contains povidone K90 with an average molecular weight of 1,100,000. High Mw povidone (>110,000) will not be excreted by the kidney and therefore will be retained in the body if repeatedly injected and may lead to serious harm;
- The PRAC noted that the risk of misuse by injection of methadone products for oral use is well-known in the target population, evidence of which is available from the literature;

- The PRAC considered that the potential for harm was likely to be associated with the misuse of methadone oral solutions containing high molecular weight povidone K90;
- The PRAC considered that the proposed risk minimisation measures to update the product information could not mitigate the known risk of misuse by the intended target population and the associated potential serious harm caused by the injection of high molecular weight povidone (K90);
- Based on the available data, the PRAC concluded, that pursuant to Article 116 of Directive 2001/83/EC the benefit risk balance of methadone oral solutions containing povidone K90 is not favourable;
- The PRAC considered the proportionate response to the evidence of harm.

As a consequence, following the provisions under Article 107j (3) of Directive 2001/83/EC, the PRAC recommends the suspension of the marketing authorisations for methadone oral solution containing high molecular weight povidone (K90).

For the suspension to be lifted, the National competent authorities of Member States shall verify that the following conditions are fulfilled by the MAH:

The MAHs should appropriately reformulate the product taking into account its misuse potential.

***Methadone tablets containing low Mw povidone (K25 or K30)***

- The PRAC considered that if low molecular weight povidone contained in methadone tablets (K25 or K30) were to be injected, it is expected to be readily excreted and not to accumulate and therefore was not associated with the potential for harm of oral solutions containing high Mw.
- The PRAC concluded that the benefit-risk of these products was favourable provided that amendments are introduced in the product information, to harmonise and reinforce the message that tablets are for oral administration only and must not be injected.

As a consequence, following the provisions under Article 107j(3) of Directive 2001/83/EC, the PRAC recommends the variation of marketing authorisations for methadone tablets containing low molecular weight povidone (K25 or K30).

**CMDh agreement**

The CMDh, having considered the PRAC recommendation dated 23 July 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the suspension of the marketing authorisations for methadone oral solution containing high molecular weight povidone (K90). The condition for lifting the suspension of these marketing authorisations is set out in Annex IV.

The CMDh also reached an agreement on the variation to the terms of the Marketing Authorisations for methadone tablets containing low molecular weight povidone (K25 or K30) for which the amendments to be introduced to the Summary of Product Characteristics and package leaflet are set out in Annex III.

The timetable for the implementation of the agreement is set out in Annex V.