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Assessment report for methadone medicinal products for oral use containing povidone

Procedure under Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1395

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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1. Background information on the procedure

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 (procedure number: EMEA/H/A-107i/1395) 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 under the provisions of Article 107i of Directive 2001/83/EC 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effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.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 triggering of the procedure was based on reports of kidney failure and other serious adverse reactions in former or current drug abusers in Norway, which led NOMA to suspend methadone oral solutions-containing povidone on their national market.

After reviewing all the available data submitted by the Marketing Authorisation Holders (MAHs) and by others Stakeholders, the PRAC adopted a recommendation on 10 July 2014.

2. Scientific discussion

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). Methadone has a well-known safety profile when used as recommended in the product information. The safety concern in question is related to the risk of misuse by injection of methadone products for oral use containing povidone.

This review was initiated following a number of reports of kidney failure and other adverse reactions (ADRs) like e.g. bone marrow disorder and anaemia, in former or current drug abusers with the suspected drug entered as the excipient polyvinylpyrrolidone (more commonly known as povidone or PVP). No trade name of a suspected drug was entered in these reports but based on further research the biopsy findings were linked to the so-called povidone storage disease, which in turn was considered to be associated with the injection of povidone of high molecular weight.

NOMA first became aware of a suspicion towards Methadone Martindale Pharma on 12th March 2014. Based on the safety concerns and further consideration of the current evidence, NOMA considered the benefit-risk balance of Methadon Martindale Pharma 2mg/ml oral solution, the only methadone product containing high molecular weight povidone available on the Norwegian national market, not favourable in the management of opioid dependence and therefore decided that this product would be suspended on 8 April 2014. Consequently, NOMA initiated an urgent union procedure under Article 107i of Directive 2001/83/EC and asked the European Medicines Agency to review the risk benefit balance of all methadone medicines for oral use containing povidone in the European Union (EU). In addition to methadone oral solutions containing high molecular weight povidone, other methadone medicinal products containing povidone, albeit in lower molecular weight and in a smaller amount, were also considered for the EU review.

Methadone products for oral use containing povidone are currently approved in 10 Member States of the Union on prescription only: Denmark, Finland, Hungary, Iceland, Malta, Norway, Romania, Spain, Sweden, and United Kingdom. A 2mg/ml oral solution containing povidone K90 is authorised in six MSs (Denmark, Finland, Malta, Norway, Sweden and the United Kingdom). The other formulations of methadone containing povidone are 5mg and 20mg tablets and contain povidone K25 or K30.

Methadone tablets containing povidone are authorised in eight MSs (Denmark, Finland, Hungary, Iceland, Norway, Romania, Spain and Sweden).

Following the initiation of the Art 107i referral procedure, the PRAC addressed lists of questions (LoQ) to all MAHs of methadone products containing povidone, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and other stakeholders, to an ad-hoc expert group, as well as to the pathologists and clinicians, who reported the individual case reports forming the basis of the signal.

2.1. Quality aspects

Povidone (polyvinylpyrrolidone, PVP) is a polymer of 1-vinyl-2-pyrrolidone. It is used in a variety of pharmaceutical formulations. Its primary use is in tablets, where povidone is used as a binder in wet-granulation processes. Another use is as a viscosity-increasing agent, which also can aid stability, in oral solutions.

Povidone is available in a variety of different molecular sizes from K12 (low molecular weight (Mw), average Mw ~ 2000) to K90 (high molecular weight, average Mw 1,100,000). The viscosity-increasing properties in aqueous solution depend on the molecular weight of povidone.

Differentiations between individual grades of different molecular weight are made on the basis of their relative viscosity in water and their K-value, which can be calculated from the former according to the European Pharmacopoeia (Ph. Eur.) monograph for povidone. In Ph. Eur. the specification for K25 is a K-value of 22.5 to 27.0 (typical range 24-27), while for K90 the specification is 81.0 to 97.2 (typical range 85-95).

Viscosity-average molecular weight can be calculated from the K-value (or alternatively in a two-step calculation from relative viscosity via intrinsic viscosity). For K25 the viscosity-average molecular weight is 25,700 if it is calculated from the nominal value or 19,300 to 31,100 if it is calculated from the typical K-value range as tabulated in the Ph. Eur. monograph for povidone. For K90 the viscosity-average molecular weight is 1,100,000 if calculated from the nominal value or 790,000 to 1,350,000 if it is calculated from the typical K-value range in the Ph. Eur. The average molecular weight may also be determined by other techniques, e.g. light scattering or gel permeation chromatography. During manufacture the polymerization process does not produce polymer of a single chain length or molecular weight. In the ideal case there is a Gaussian distribution of molecular weights.

The methadone tablets concerned by this review contain a low amount of povidone K25 or K30, used as binders in wet-granulation processes. The methadone oral solutions concerned by this review contain povidone K90, used as a stabiliser and viscosity enhancer.

2.2. Pharmacology, Pharmacokinetics and toxicology of povidone

2.2.1. Pharmacology/Pharmacokinetics

Insignificant amount of povidone is absorbed following oral administration. When administered by oral route, this excipient is inert and non-toxic, passes through the gastrointestinal tract and is excreted.

The distribution and elimination of povidone when taken intravenously in various species was quite extensively studied during the 1950s and 1960s. It seems generally accepted that povidone tissue retention and excretion is dependent on the molecular size. Some of the relevant non-clinical and clinical literature is summarised below.

Hespe et al. (1977)¹ described the effects on distribution and excretion in rats of two ¹⁴C- povidone preparations both with low Mw but differing Mw distributions. In preparation A, 5% of the particles had a Mw > 25,000, and in preparation B, 0.5% of the particles had a Mw > 25,000. Each of the preparations was administered intravenously at 50 or 200 mg/kg to rats. During the 72-hour period following administration of 50 mg/kg, radioactivity was distributed in excreta. For preparation A, 92.6±11.3% of the administered dose was detected in the urine, 7.0±6.3% in faeces, and 0.43±0.04% as respired CO₂. For preparation B, 93.1±4.6% of the administered dose was detected in the urine, 4.4±3.4% in faeces, and 0.47±0.01% as respired CO₂. By day 22, 86% of the administered amount of preparation A and 92.2% of preparation B had been recovered (not statistically significant). Analysis of the bile collected for 5 hours post dose showed a recovery of 1.2 and 1.9% of the administered dose of preparation A and B, respectively.

Distribution as assessed by autoradiographs six days after administration showed high levels of radioactivity in kidneys and the gastrointestinal tract of animals dosed with either preparation. High levels were also detected in the urinary bladder, liver, spleen, pancreas, skin, sclera, connective tissue, bone marrow and joints in animals administered preparation A while levels in the same organs were difficult to detect in animals given preparation B. The authors concluded that preparation A was more retained in the body and excreted to a lesser amount than preparation B. The difference was attributed to the different Mw distribution with preparation A having a higher fraction of particles > 25,000 regarded as the limit for rapid glomerular filtration in the rat. This study also showed that the major excretion route for povidone is via urinary excretion. However, the high levels of radioactivity in the gastrointestinal (GI) tract and the detection of low levels of radioactivity in bile indicate that a fraction of povidone is eliminated via biliary excretion. A molecular weight range of 6,000 to 10,000 has been suggested as an upper limit for povidone biliary excretion in the rat (Rozé et al, Ann. Pharmac. Franc. 29:513-520, 1971).

Distribution, metabolism and excretion of ¹⁴C- or ¹³¹I-labelled povidone fractions with different Mw (K23 up to K50) after a single intravenous dose were studied in rats, rabbits, dogs and humans by Ravin et al. (1952)². A similar distribution pattern of povidone K33 was observed in all three species. The skeletal muscle, skin and subcutaneous tissue contained the largest fraction but lowest concentration of povidone; the organs of the reticuloendothelial system (RES) (liver, spleen, bone marrow and lymph nodes) had the highest concentration. The amount retained in the skeletal muscle, skin and subcutaneous tissue decreased progressively, while that retained in the RES system remained almost constant during the observation period up to 6 months indicating that the turnover in the RES is very slow.

The effect of the molecular weight on retention was further examined by separating a sample of K30.2, ¹⁴C- povidone into K27 and K37 fractions (analysis determined that 23% of the K30.2 sample had a mean Mw of 117,000). Groups of rats were infused with 35 mg of either fraction or the original unfractionated solution, and terminated after 2 weeks. Overall, tissue retention was greater with increasing K-value. Most significant was the finding that the retention in the spleen (representative of the RES) increased with increasing K-value disproportionately to retention in other organs. An estimated 10% of the un-fractionated povidone was retained in the RES. Based on this, it was concluded that molecules with a Mw > 117,000 were retained in the RES. In humans, it was determined that the K-value of povidone excreted in the urine within the first 6 hours was lower than the K33 of the infused preparation. The K-value of urinary povidone rose 48-96 hours following infusion to peak corresponding to a Mw of 40 000. Povidone (Mw between 40,000 and 120,000) continued to be

¹ Hespe W, Meier AM, Blankwater YJ. Excretion and distribution studies in rats with two forms of ¹⁴carbon-labelled polyvinylpyrrolidone with a relatively low mean molecular weight after intravenous administration. *Arzneimittel-Forschung*. 1977; 27(6):1158-62. Epub 1977/01/01.

² Ravin HA, Seligman AM, Fine J. Polyvinyl pyrrolidone as a plasma expander; studies on its excretion, distribution and metabolism. *The New England journal of medicine*. 1952; 247(24):921-9. Epub 1952/12/11.

excreted at the rate of 25 mg/day (0.06% of a clinical dose of 17.5 g) for as long as 1 year. Whether this long-term excretion of povidone (Mw 40,000 and 120,000) takes place by filtration through a limited number of large pores or via a different mechanism is unclear. Approximately 0.3 to 0.5% of the administered dose appeared in faeces within 24 hours and it then declines to an average of 0.001% per day.

Others also report that approximately 0.3% of intravenously administered povidone doses are excreted in the faeces of healthy persons (Bossekerk and Keil, E. Klin. Wschr. 40: 851-853, 1962). Between 0.15 and 0.20% of the dose was found in the expired air during the first 12 hours in man, and it then fell to 0.01% in subsequent 12 hour periods. At 36 hours, no radioactivity was detected in the respired air. It was concluded that there was no significant metabolic degradation of povidone and no significant route of excretion except via the kidneys.

Further information on the relationship of molecular size and renal excretion is described by Hulme and Hardwicke (Clinical Science 34:515-529, 1968). The authors showed that the normal glomerulus of rabbits and healthy human subjects was highly permeable to povidone with a Mw <30,000 but relatively impermeable to those with a Mw >70,000. In a review by Wessel et al (Arzneim.-Forsch.Drug Res. 21:1468-1482, 1971), a summary on povidone elimination in animals and man based on 23 publications between 1952 and 1969 was presented. After intravenous administration, povidone Mw <20,000 was completely eliminated via kidneys and 85-90% of the dose was excreted within the first 3 days. The remaining 10-15% passed temporarily from blood to the lymph and tissues and was excreted within a few days. Povidone with Mw >30 000 was eliminated after a delay and partly retained for weeks to months. It was concluded that the povidone elimination was clearly inversely related to molecular weight. The authors also noted discrepancies in the published literature concerning the renal threshold for povidone (reports of limits have ranged from 25,000 to 70,000). These may partly be due to an assumption of Mw based on trade name in many of performed studies. In addition, there seems to be difficulties in confidently ascribing a Mw to a particular grade of povidone because of a past lack on industry-wide agreement on methodology.

2.2.2. Non clinical toxicology

The toxicity profile of povidone was described in various non-clinical species and in humans. The available non-clinical literature considered of relevance is summarised below.

- BIBRA Toxicological International (1991)

A publication by the British Industrial Biological Research Association (BIBRA) Toxicology International (1991)³ reviewed the toxicity profile of povidone. In this publication, references are given to articles from the 1950's where single intravenous injections of povidone (Mw 40,000) at 0.5 to about 3 g/kg body weight (bw) caused mild abnormalities and povidone storage in a wide range of tissues. Repeated injection (typically 1-3 L of 3.5% in saline [approximately 0.6-1.7 g povidone/kg bw], but up to 5.6 g/kg bw on occasions) has been used extensively with no clear evidence of adverse effects, however, the molecular weight was not reported.

BIBRA also referred to articles from the 1970's-1980's where deposits identified as povidone were found in RES cells (also called macrophage system or mononuclear phagocyte system) of various organs and in the lung, kidney and intestines when administered in very large amounts or over long periods (either as a plasma replacement or as a drug carrier).

³ BIBRA monograph polyvinylpyrrolidone1991. Available from:
<http://legacy.library.ucsf.edu/documentStore/t/h/e/the22d00/Sthe22d00.pdf>.

According to BIBRA, microscopic examination revealed slight structural changes in various tissues including the kidney and lymph nodes at doses of about 20-70 g [about 0.3-1.2 g/kg bw], whereas more severe effects, were seen at doses of about 200 g or above (Kojima et al. 1967⁴). Slight adverse effects on the function of lungs, kidneys, liver and intestines, in association with povidone storage in these organs, have been described in a group of 54 patients following total doses of 70 g or more [approximately 1.2 g/kg bw] given to replace plasma (Honda et al., 1966⁵).

BIBRA also identified publications concerning adverse effects on the structure or function of different tissues following total doses apparently of 10 g/kg bw or greater (Basset et al. 1971⁶; Delbarre et al. 1964⁷; Mazieres et al. 1980⁸; Reske-Nielsen et al. 1976⁹).

This review of the toxicity profile supports that repeated intravenous injections of povidone creates deposits in several tissues including kidneys. However, information of impaired function of organs is lacking as well as information regarding molecular weight.

- Other publications

In mice, Frommer (Am. J. Path. 52:433-453, 1956) quantified abnormal macrophages (foam cells) in the liver following single- and repeated doses of various amounts and molecular sizes of povidone (K20, Mw 20,000; K30, Mw 40,000; and K71, Mw 125,000) after intravenous, intraperitoneal or subcutaneous administration. Foam cells (~1%) were observed in the liver 30 days after a single injection (presumably i. v.) of 17.5 mg povidone (Mw 40 000) and of 25 mg povidone (Mw 125,000) but not after 100 mg povidone (Mw 20,000). In the same study, repeated administrations (up to 20 injections over a 24-day period) of the various povidones were studied. The foam cell liver content at the highest dose (500 mg) of the high Mw povidone was estimated to 68%. The author concluded that the ratio of foam cell production induced by 100 mg of povidone of low, medium and high Mw was approximately 1:2:6 indicating that foam cell production is a function of molecular size.

In the same experimental setting, Frommer (Proc. Soc. Exp. Biol. Med. 86:567-699, 1954) used the bromosulphalein (BSP)-retention test to determine if changes in mouse liver function occur after intravenous, intraperitoneal, or subcutaneous administration of povidone of various molecular size (K20, K30 and K71) for 1 to 7 injections. No changes in BSP-retention were observed at various time-points between 3 and 60 days after last administration, indicating a normal liver function.

In rabbits receiving 16 intravenous injections povidone (Mw not reported) over a 2-month period, gross necropsy revealed enlarged spleens (~70%) (Nelson & Lusky, Proc. Soc. Exp. Biol. Med. 76:765-767, 1951). Microscopic pathology revealed the presence of foam cells primarily in the spleen where they made up an estimate of 30 to 50% of the organ volume. Foam cells were also present in a moderate degree in the lymph nodes, bone marrow and adrenal medulla and in a lesser degree in the liver, lungs and thymus. No effects of treatment on behaviour or body weight were noted. Blood count or chemical analysis was not studied.

⁴ Kojima M, Takahashi K, Honda K. Morphological study on the effect of polyvinyl pyrrolidone infusion upon the reticuloendothelial system. The Tohoku journal of experimental medicine. 1967;92(1):27-54. Epub 1967/05/01.

⁵ Honda K, Hanzawa K, Watanabe N, Koseki M, Watanabe M. Massive hemorrhage from high superficial gastric ulcer. International surgery. 1966;45(4):362-6. Epub 1966/04/01.

⁶ Basset F, Bocquet L, Chabot J, Paolaggi JP, Delbarre F. [A case of polyvinyl disease. Anatomical study]. Annales d'anatomie pathologique. 1971;16(2):159-72. Epub 1971/04/01. A propos d'un cas de maladie polyvinylique. Etude anatomique.

⁷ Delbarre F, Paolaggi JB, Basset F. ["Artificial" Thesaurismosis Caused by Polyvinylpyrrolidone. Report of 2 Cases]. Bulletins et memoires de la Societe medicale des hopitaux de Paris. 1964;115:243-58. Epub 1964/02/07. Thesaurismose "artificielle" par polyvinyl-pyrrolidone. pr'esentation de deux cas.

⁸ Mazieres B, Durroux R, Jambon E, Bouteiller G, Arlet J. [Bony condensation and necrosis of the femoral head due to polyvinylpyrrolidone thesaurismosis (diagnostic discussion with histiocytosis X)]. Revue du rhumatisme et des maladies osteo-articulaires. 1980;47(4):257-65. Epub 1980/04/01. Densification osseuse et necrose de la tete femorale par thesaurismose a la polyvinyl-pyrrolidone (discussion diagnostique avec l'histiocytose X).

⁹ Reske-Nielsen E, Bojsen-Moller M, Vetner M, Hansen JC. Polyvinylpyrrolidone-storage disease. Light microscopical, ultrastructural and chemical verification. Acta pathologica et microbiologica Scandinavica Section A, Pathology. 1976;84(5):397-405. Epub 1976/09/01.

Hueper (J. Natn. Cancer Inst. 26:229-237,1961) studied povidone with different molecular sizes after repeated intraperitoneal administration in rats and rabbits. The study included 2 test povidones (K17, Mw 2,000 to 38,000 and K25, Mw 4,000 to 80,000 and 2 control povidones (mean Mw 50 000). The povidone preparations were administered at 2-week intervals to rats and rabbits. Rats (n=35/group) received in total 4 injections (in total 2 g) and rabbits (n=6) up to 5 injections (in total 62.2 g) of povidone K17 and K25, respectively. In addition, rats were also given a total of 15 injections (in total 15 g) of the 2 control povidones. Control rats and rabbits receiving saline were also included in the study. Rats and rabbits were terminated after 2 years and 28 months, respectively, and histological examination was performed on all tissues with any macroscopical abnormalities (H/E staining). The most prominent histopathological finding was the presence of light-blue-, deep-blue- or slate-blue stained homogenous matter within foam cells as well as in the form of extracellularly located "lakes" in various tissues such as the lung, heart, aorta, pulmonary artery, spleen, pancreas, choroid plexus, ovary, uterus adrenal gland, liver, kidney and stroma of some cancer tumours. The foam cell deposits were observed in rats injected with all 4 povidones but in rabbits, only those receiving the K25 povidone. Blood analysis (bleeding time, coagulation time and sedimentation rate) did not reveal any acute or chronic effects. The authors speculated that the noted species differences in foam cell development between rats and rabbits may be due to species differences in the permeability of the glomerulus.

2.2.3. Clinical toxicology

A literature review was performed by the MAHs identifying a number of articles describing povidone storage and adverse effects. The available literature considered of relevance is summarised below.

Honda et al. (1966)¹⁰ studied complications following use of povidone in Japan. They examined 144 cases where 3.5% middle Mw (not specified) was used as a plasma expander in subjects with chest, abdominal and other diseases who were divided into 4 groups according to the quantity of povidone used (A: <69g, B: 70-99g, C: 100-139g and D: >140g). Complications were classified as pulmonary (sputum, haemoptysis, etc.), hepatic (jaundice), renal (proteinuria, haematuria, etc.), intestinal (hematemesis, tarry stool, etc.), wound (wound opening, unhealthy granulation, etc.), and general complications (weakness, anorexia, fatigue, fever, etc.). Of the 144 cases, there were 31 deaths and autopsy was performed in sixteen of them. Based on the results of comparing autopsy findings with complications observed before death, the authors concluded that in the cases which showed severe pulmonary, hepatic, renal and intestinal complications, high storage of povidone had been found in these tissues. In the cases with wound and general complications, storage of povidone was found in the bone marrow, lymph nodes, and spleen. They concluded that administration of povidone should be avoided as much as possible, but if necessary, less than 69g of it should be administered.

Huang WC et al. (2012)¹¹ reported femoral fracture and anaemia with povidone storage disease in a 65-year-old female patient after several years of povidone treatment for "nutrition support".

Dunn et al. (1998)¹² described a case in a 39 year old woman suffering from myelofibrosis, heavy infiltration of histiocytes and povidone storage disease after receiving 50 infusions of 500 ml 5% povidone prescribed by an illegal doctor. Other differential diagnoses were excluded. No recovery was

¹⁰ Honda K, Hanzawa K, Watanabe N, Koseki M, Watanabe M. Massive hemorrhage from high superficial gastric ulcer. *International surgery*. 1966;45(4):362-6. Epub 1966/04/01.

¹¹ Huang WC, Chang CH, Tsai CC. Polyvinylpyrrolidone storage disease presenting as pathologic fracture and anemia: report of a case with imprint cytology. *Diagnostic cytopathology*. 2012;40(1):69-72. Epub 2011/12/20.

¹² unnn P, Kuo T, Shih LY, Wang PN, Sun CF, Chang MJ. Bone marrow failure and myelofibrosis in a case of PVP storage disease. *American journal of hematology*. 1998;57(1):68-71. Epub 1998/01/10.

noted 5 years after discontinuation of povidone infusion. This case report indicates that infusion of excessive amounts of povidone can cause bone marrow failure.

Kepes et al. (1993)¹³ described "mucoid dissolution" of bones and multiple pathologic fractures in a 52-year-old woman in Taiwan with a past history of intravenous administration of povidone. She had received repeated intravenous injections of povidone as a plasma expander (Mw not specified) for 10 years, and suffered pathologic fractures of both femora and her right humerus with additional destructive lesions seen radiologically in other bones. Biopsies of the fracture sites showed intracellular povidone deposits and mucoid changes in the involved cells, a characteristic secondary complication of povidone deposition. This phenomenon, if of sufficient severity, may cause, as in this case, a virtual 'melting down' of osseous tissue with pathological fractures.

Kuo et al. (1997)¹⁴ described two cases of severe anaemia and serious orthopaedic complications due to massive infiltration of povidone-containing cells in the bone marrow with destruction of bone after povidone was given inappropriately by intravenous injection as a "blood tonic". The first case concerned a 60 year-old female who, in addition to cutaneous povidone storage, had severe anaemia and hip joint destruction. A bone scan showed multiple active lesions. The second case concerned a 43 year-old female for which was reported severe anaemia and vertebral bone destruction. In this case too, the bone scan showed multiple active lesions. The bone marrow biopsy specimens of the two patients showed almost total replacement of the bone marrow by massive infiltrates of blue-grey vacuolated povidone storage cells. Only focal residual hematopoietic cells remained. The anaemia was irreversible and no therapy could be offered to correct the underlying problem. The injected solution contained 53mg/ml of povidone.

In none of the above case reports was the molecular weight of the administered PVP stated.

On 19 April 1978 the Food and Drug Administration (FDA) approval for Polyvinylpyrrolidone in Normal Saline was withdrawn since it was found to be unsafe for use as a plasma expander in the emergency treatment of shock. This was based on the fact that povidone accumulates in the body and may cause storage disease with the formation of granulomas. Povidone was also considered to interfere with blood coagulation, haemostasis, and blood typing and cross matching (Federal Register of April 7, 1978 (43 FR 14743)).

Discussion and conclusions on pharmacology and toxicity of povidone

Povidone was initially used as a plasma expander.

Available non-clinical studies mainly published between 1950s and 1970s consistently describe that parenterally (intravenously, intraperitoneal or subcutaneous) administered povidone is retained in various tissues in mice, rats and rabbits for long periods.

Using radioactive labelled povidone of different molecular weight, it has been demonstrated that clearance of polymers after intravenous administration is dependent on molecular weight. Following parenteral administration, low molecular weight povidone (Mw <25 000) is generally accepted to be readily and almost completely excreted by the kidneys. Higher Mw povidone, however, is not (Mw >110,000), or only partially (Mw > 40,000) excreted. The distribution of povidone seems similar in rat, rabbits and man and the highest concentrations and retention were detected in the organs of the RES (liver, spleen, bone marrow and lymph nodes). In addition, it has been observed that mesenchymal

¹³ Kepes JJ, Chen WY, Jim YF. 'Mucoid dissolution' of bones and multiple pathologic fractures in a patient with past history of intravenous administration of polyvinylpyrrolidone (PVP). A case report. Bone and mineral. 1993;22(1):33-41. Epub 1993/07/01.

¹⁴ Kuo TT, Hsueh S. Mucicarmophilic histiocytosis. A polyvinylpyrrolidone (PVP) storage disease simulating signet-ring cell carcinoma. The American journal of surgical pathology. 1984;8(6):419-28. Epub 1984/06/01.

tissues rich in macrophages (skin, muscle and connective tissues) also store povidone in large quantities as a result of incorporation by pinocytosis. This gives rise to the vacuolated appearance which has led to the description “foam cells”.

A few publications described normal organ function and no evidence of toxicity despite the presence of foam cells. Despite the high retention reported in some studies, the non-clinical toxicological consequences of the observed povidone deposits have not been fully established. The BIBRA review of toxicity profile supports that repeated intravenous injections of povidone creates deposits in several tissues including the kidneys. It is however acknowledged that in various studies information of impaired organ function and on the molecular weight of povidone is lacking.

Available data from the scientific literature suggest that infusion of excessive amounts of povidone can cause bone marrow failure. It also indicates that intracellular povidone deposits in the bone tissue can cause mucoid changes in the involved cells, which may, if of sufficient severity, affect the osseous tissue with pathological fractures as a consequence.

The mechanism of pathophysiology appears to be related to the replacement of functionally active tissue by povidone.

2.3. Clinical safety and efficacy of methadone for oral use

2.3.1. Clinical efficacy

The efficacy of methadone opioid substitution treatment (OST) was acknowledged in this referral procedure. The overall effectiveness of methadone maintenance treatment is established. Flexible-dose methadone maintenance therapy is more clinically effective than no drug therapy in dependent opiate users (Connock et al., 2007¹⁵). Mattick et al. (2009)¹⁶ presented a Cochrane review which concluded that there is a superiority of methadone over control in retaining patients in treatment (4 studies, 750 patients, RR= 4.44, 95% CI: 3.26-2.04). The results also showed a trend in favour of methadone over control regarding mortality although the difference was not statistically significant (4 studies, 576 patients RR=0.48, 95% CI: 0.10-2.39).

2.3.2. Clinical safety

Post-marketing safety data related to povidone in methadone products and data from the EMCDDA on the misuse of these products were considered in this review. These data are hereafter presented and discussed.

- Misuse by injection of methadone products for oral use

The definition of an adverse reaction as stated in article 1 of Directive 2001/83/EC, is a response to a medicinal product which is noxious and unintended. This includes reactions that arise from use outside of the terms of the marketing authorisation, including overdose, off-labels use, misuse, abuse and medication errors (Good Pharmacovigilance Practices (GVP) Module VI). It follows that misuse of a medicinal product, in this case by injection of methadone products for oral use, is considered within the scope of the pharmacovigilance legislation, and should be reported, monitored, assessed and any action taken as necessary, as for any safety issue related to a medicinal product.

¹⁵ Connock M et al. Health Technol Assess 2007; 11(9).

¹⁶ Mattick RP et al. Cochrane Database Syst Rev. 2009 Jul 8; (3).

Although the MAHs who were involved in this review were not notified of any adverse reaction reports concerning misuse, the intravenous injection of methadone intended solely for oral use is widely described and is well-known to organisations in charge of OST programs. This was confirmed by the experts of the ad-hoc expert group.

Misuse by injection of methadone is also reported in the literature but its frequency is difficult to establish considering the nature of the non-compliance and the differences in methods used to identify subjects. The occurrence of injection of methadone for oral use among injecting drug users seems to vary between 5.0% to 79.5% (Winstock et al. 2010¹⁷, Guichard et al. 2003¹⁸, Waldvogel et al. 2005¹⁹, Judson G et al. 2010²⁰, and Vlahov D et al. 2007²¹). The extent of the misuse by injection of methadone products for oral use varies substantially by jurisdiction. In addition, it is most likely that misuse in drug abusers is underreported.

Data from the EMCDDA, following an ad hoc consultation with its National Focal Points in the European Economic Area (EEA) (21 countries) in May 2014, shows that injection of oral methadone products:

- Is common: 1 country
- Occurs, but rarely: 6 countries
- Is extremely uncommon: 6 countries
- Never happens: 5 countries
- Is of unknown frequency: 3 countries

EMCDDA monitoring data were collected for clients entering treatment in specialised treatment centres in 2011 or 2012. About 1.74 % (7681 individuals) of the clients entering treatment programs entered treatment for primary misuse of methadone. EMCDDA estimates the number of clients injecting (misusing) methadone as primary drug to 627 individuals in the EEA (based on data from 2011 or 2012).

- Serious adverse reactions

NOMA received in total 15 cases with serious adverse reactions²² concerning former or current injecting drug users, aged 24 to 53 years old. Most of the patients were currently or previously included in OST programs. In addition to failure of various organs, all the 15 cases reported "intentional drug misuse", "product deposit" and "drug administered via inappropriate route". These cases were assessed as possibly or probably related to injected povidone by the regional pharmacovigilance centre.

The suspected substance, povidone, was identified with biopsies taken from these patients due to organ failure or during autopsy that showed macrophages containing material consistent with povidone. This identification was based on H&E, Congo Red and periodic acid methenamine silver staining. The results of the staining were the same for the majority of the reports: Periodic acid-silver methenamine (PASM): black, Congo red: red (pink to brownish-reddish), H&E: grey-blue. Specifically, in addition to the routinely performed H&E staining, 19 biopsies from the reported 15 patients were stained with Congo Red and 15 biopsies with PASM. The staining results were positive (i.e. consistent with povidone) in all cases.

¹⁷ Winstock AR, Lea T. Diversion and injection of methadone and buprenorphine among clients in public opioid treatment clinics in New South Wales, Australia. *Substance use & misuse*. 2010; 45(1-2):240-52. Epub 2009/12/23.

¹⁸ Guichard A, et al. *Addiction*. 2003 Nov; 98(11):1585-97.

¹⁹ Waldvogel D, et al. *Swiss Med Wkly*. 2005 Oct 29; 135(43-44):644-6.

²⁰ Judson G, et al. *Drug Alcohol Rev*. 2010 Jan; 29(1):41-6.

²¹ Vlahov D, et al. *Addiction*. 2007 May; 102(5):771-7.

²² The number of ICSRs reported to NOMA is, per 26th June 2014, 15. The number of cases is evolving, as more cases are identified. In their responses to the PRAC LoQ, the pathologists at HUS referred to 16 and/or 17 cases, and even 19 in a presentation dated 16th June 2014. Due to lacking patient information, these cases are not included in this review. The conclusions in this assessment report are based on the 15 ICSRs received by NOMA.

In fourteen (14) of these fifteen (15) cases the reported adverse events included renal failure. 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 other biopsies from these patients. For five patients, bone destruction and/or bone marrow affection (including anaemia) were reported associated with findings in biopsies. 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 patients, with deposits of povidone also in the bone marrow.

For twelve (12) of the fifteen (15) patients, evidence for prescription or use of 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 the nine cases a history of injecting methadone intended for oral use was reported. No brand of methadone product could be identified although in one case the patient had been prescribed Methadone Martindale Pharma and the misuse of this product was strongly suspected.

An overview of the cases reported by NOMA is given in the table below.

Table 1. Summary of the 15 cases reported by the Norwegian Medicines Agency^a

ID No.	Age	Sex	Included in OST	History of injection	Substances identified in urine-screening *	Adverse event	Biopsy #	Co-morbidity
2013-16395	46	F	Not included	Amphetamine and methadone	Several benzodiazepines, methadone, buprenorphine and cannabis	Renal failure	Kidney	hypertension
2014-17613	35	M	2004	Buprenorphine methadone and a number of illegal substances	Not specified	Fracture of clavicle and colli femoris, bone marrow failure, anaemia, renal failure	Bone marrow, clavícula and stomach	
2013-16398	41	M	2008-	Heroin	Not specified	Renal failure, weight loss, fracture of clavicle	Clavícula and bone marrow	Hepatitis C
2014-17650	24	M	2013	Heroin, buprenorphine and methadone	Several benzodiazepines, heroin-metabolites, metadone and cannabis	Renal failure and multiorgan failure	Skin	
2013-16399	37	M	2007	Heroin, buprenorphine, methadone, imovane and amphetamine	Amphetamine, methadone, diazepam and cannabis	Renal failure	Kidney	
2013-16397	39	M	2010	Heroin, suspected methadone	Cannabis, amphetamines and different benzodiazepines detected. A few samples with oxycodone	Enlarged lymph nodes, stomach pain, renal failure and weight loss.	Bone marrow, lymph node, gastric, duodenal, ileal and colonic	Hepatitis C
2013-16400	31	M	2008	Methadone probably Martindale	Cannabis different benzodiazepin, amphetamine/methamphetamine, heroin-metabolites.	Anaemia and renal failure	Bone marrow	Hepatitis C
2013-16393	45	M	2012	Temgesic, Dolcontin, methadone and heroin.	Morphine, amphetamine, heroin-metabolites	Renal failure and anaemia	Kidney, bone marrow	
2014-17652	33	F	2009	Temgesic, heroin, methadone	Buprenorphine, benzodiazepines, cannabis and opiates	Renal failure	Skin	
2013-16390	44	M	Not defined	Not specified	Not specified	Renal failure	Kidney	

ID No.	Age	Sex	Included in OST	History of injection	Substances identified in urine-screening *	Adverse event	Biopsy #	Co-morbidity
2013-16391	53	M	Not defined	Not specified	Not specified	Renal failure	Kidney	Hepatitis C
2013-16392	33	M	Not defined	Not specified	Not specified	Renal failure	Kidney	Hepatitis C
2014-17651	46	M	2011	Not specified	Not specified	Fatal, weight loss, anaemia, lymphadenopathy and multiorgan failure	Lymph nodes, intestine and rectum	
2013-16394	36	M	Not defined	Not specified	Cannabis, amphetamines, heroin-metabolites and diazepam-metabolites	Not specified	Bone marrow and intestinal wall	Hepatitis C
2013-16396	34	M	2007	Not specified	Clonazepam, amphetamine, cannabis, heroin metabolites, methamphetamine, several benzodiazepines	Multi-organ failure, anaemia. Fatal outcome due to bronchopneumonia suspected as a consequence of bone marrow disorder.	Bone marrow and autopsy	

^a The cases were reported during 2013-2014 but the biopsies were collected between 2009 and 2014.

* (prescribed substances excluded)

(all biopsies have demonstrated deposits of polymer)

OST = opioid substitution treatment

Discussion and conclusion on clinical safety

In Norway 15 cases with povidone deposits demonstrated in biopsies or autopsy samples have been reported among subjects with former or current drug abuse. The reported adverse reactions included e.g. renal failure (14 cases), anaemia (5 cases) and pathologic fracture (2 cases). In all cases, staining of biological samples supported the conclusion that povidone accumulated in the affected organs.

In seven of these cases, povidone deposits (histiocytic infiltration) were detected in the bone marrow and bone destruction and/or anaemia were specifically reported in five of these patients. 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. These adverse effects are similar to the cases described in the literature. It is therefore considered that these cases indicate a likely association between povidone and the adverse reactions.

For other organs such as the GI tract and kidneys the causative association with povidone is considered less strong. The reported GI symptoms (pain, diarrhoea, weight loss) are unspecific and could have other aetiologies, e.g. malnutrition. As regards the kidneys, although povidone deposits were found in renal interstitial areas with tubular atrophy and fibrosis, it cannot be conclusively proven that povidone was the cause of tubule-interstitial damage. In some of the kidney biopsies there was additional pathology present in the form of vascular changes unrelated to povidone storage. It cannot be ruled out that these latter changes may have caused hypo-perfusion of the kidney, which in turn could have affected the tubule-interstitial areas. In addition, there is a lack of detailed clinical data, especially regarding the degree of proteinuria and creatinine clearance, in the majority of the reported cases. Therefore, although it is possible that the renal damage may be related to povidone, the pathological results could not completely exclude other causes, e.g. injections of other drugs.

An ad-hoc expert group meeting was held during this review and the experts consulted considered that there is strong evidence that the deposits found in the bone marrow were deposits of povidone. The existence of the deposits was recognized as a potential safety concern.

Eight reported cases documented a history of intravenous injection of methadone intended for oral use. From the reported cases it could not be stated which brand of methadone has been used. In one case there is a strong suspicion that methadone containing high molecular weight povidone (Methadone Martindale Pharma) has been misused as intravenous injection of the product intended for oral use. The experts consulted confirmed that, in line with published literature, misuse by injection of methadone product is an inherent risk in the target population.

The PRAC considered it reasonable to assume that the povidone deposits have come from intravenous injection of high Mw povidone, supported by the knowledge from literature that intravenously administered povidone is excreted via the kidneys and the clearance depends on molecular-weight, i.e. low molecular weight (Mw <25,000) is excreted but high molecular weight (Mw >110,000) is retained in the body.

The lack of data regarding brand names due to the difficulties to obtain reliable information regarding previous exposure (based on the illicit nature of abuse and misuse) is acknowledged. However, it was noted that the only high molecular weight povidone-containing oral methadone product available in Norway was Methadone Martindale Pharma oral solution 2mg/ml (Mw 1,000,000-1,500,000). It contains 11.7 mg/ml high molecular weight povidone (K90) and was the only oral povidone containing methadone product on the Norwegian market before 2mg methadone tablets containing a lower molecular weight povidone (K25) became available in June 2013. In addition, Methadone Martindale Pharma oral solution 2 mg/ml constituted 47-56 % of the oral methadone provided via the OST program in the region of Norway where the cases were reported in the period 2009-2011, and about 26% in 2012.

No other reports were identified in the European EudraVigilance database or in the WHO Adverse Drug Report (ADR) database. However, the absence of other reported cases can be expected due to the higher exposure of Methadone Martindale Pharma in Norway compared to the other Member States where methadone oral solution containing povidone is marketed; the level of underreporting of misuse in drug abusers; and the low likelihood of both detecting povidone deposits and making a connection between those deposits and drug abuse and reporting the suspected ADR to the national pharmacovigilance systems.

2.4. Risk minimisation activities

Methadone oral solution containing high MW povidone

In view of the safety concerns raised with the intravenous injection of povidone, the MAHs proposed a number of risk minimisation activities.

The MAH of the methadone oral solution containing povidone argued that the product information (PI) already has clear warnings advising of the potential serious outcomes if the oral solution is injected intravenously, but proposed to make it more prominent, notably on the bottle. The MAH emphasised that the oral solution was designed to be used within a framework of psychological and social counselling but acknowledged that further educational materials may help both patients and clinical services to avoid illicit use and diversion of the oral solution.

The MAH suggested that high levels of diversion and misuse of prescribed OST medication in a particular jurisdiction are linked to gaps in service provision, such as restricted access to OST treatment, inadequate doses of OST and non-existent or inadequate supervision of administration. The MAH also considered that access to low threshold harm reduction services, including needle exchange and advice, may also be important and note that English-language drug user forums routinely advise

against the injection of oral liquid methadone. Measuring the effectiveness of risk minimisation measures was also proposed.

The MAH further explained that the group of patients that receive OST are drug users and misuse of medicinal products, relapses and non-compliance are well-known risks in this population. Therefore the design of medicinal products intended to treat this patient group has to consider this risk. Povidone had been included in the formulation of the methadone oral solution to increase its viscosity, with the aim to reduce the risk of misuse.

The PRAC noted that no clinical data have been however provided to demonstrate the effectiveness of povidone in term of reducing the risk of injection and in view of the available safety data, the inclusion of high Mw povidone is considered not appropriate to reduce the risk of misusing the oral solution by injection. In addition, post-marketing data suggest that the use of povidone with high molecular weight in products intended for this group of patients is not suitable since it leads to serious adverse effects when injected intravenously. Based on the data available, the PRAC, having considered the MAH's proposed risk minimisation activities, was of the opinion that since the misuse of injecting methadone intended for oral use concerns intentional misuse and illicit use, direct information to the patients is challenging and therefore, the proposed amendments to the Product Information and labelling would not be sufficient to reduce the risk of misuse and consequently the potential risk of povidone storage disease to an acceptable level. The experts consulted in the context of the ad-hoc expert group meeting were also of the view that although information about the risks of drug misuse is very important and useful for patients, a causal relation between information provided and changes in behaviour is limited.

Concerning the supervised intake of methadone, it is only common in some jurisdictions, while take-home doses are more commonly used in others. Stricter control than currently in place in the member states, and increased supervision of methadone intake for all patients included in the OST program was considered by the PRAC but it was concluded that a stricter policy would be difficult to incorporate in everyday practice in all OST centres and may represent an increase in non-compliance.

Therefore, the PRAC considered that an appropriate reformulation of the products, taking into account their potential misuse, is necessary to effectively minimise these risks.

Methadone tablets containing low Mw povidone

Routine risk management has been conducted since first marketing authorisation. Based on the above assessment, no additional risk minimisation measures are deemed necessary for these products.

However, the PRAC recommends amendments to the PI for methadone tablets containing low Mw povidone to harmonise and reinforce the message that tablets are for oral administration only and must not be injected. The PRAC therefore proposed amendments to section 4.2 of the Summary of Product Characteristics (SmPC) to emphasize the appropriate route of administration and advise against the injection of the product. Section 3 of the Package Leaflet (PL) was amended accordingly. The PRAC also advised that further information on the type of povidone (e.g. povidone K25) should be reflected in section 6.1 of the SmPC.

2.5. Benefit-risk assessment

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 treatment (OST).

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 the 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).

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 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.

3. Overall conclusion

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

The PRAC considered 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. These considerations, in addition to the acknowledged difficulty of adequately mitigate the well-known risk of misuse in the target population led the PRAC to conclude 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 povidone of low molecular weight (K25 or K30)

With regards to these methadone products (tablets), the PRAC concluded that their benefit-risk 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.

4. Communication plan

The PRAC agreed that a direct healthcare professional communication (DHPC) should be disseminated to healthcare professionals such as physicians, pharmacists, opioid substitution therapy (OST) centres and others who are in contact with drug users and opioid maintenance treatment (OMT) patients, to inform them of the suspension of methadone oral solution containing povidone of high Mw.

The exact content and presentation of the DHPC should reflect the below key elements and is to be agreed with the national competent authority of the Member States where the product is marketed:

- Methadon Martindale Pharma oral solution 2 mg/ml will be suspended due to potential serious adverse reactions (some with possible fatal outcome) following misuse by injection
- Patients on Methadon Martindale Pharma oral solution 2 mg/ml should be switched to an alternative methadone product
- Methadon Martindale Pharma oral solution 2 mg/ml contains high molecular weight povidone K90
- High molecular weight povidone K90 is harmless when taken orally. However, if injected, povidone K90 will be retained in the body and may cause tissue damage.
- Cases of povidone deposits and serious adverse events (e.g. anaemia, pathological fractures) have been reported in drug abusers. The source of povidone cannot be confirmed, but is likely to be methadone oral solution containing high molecular weight povidone misused by injection.

5. Conclusion and grounds for the 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).