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PRAC List of questions

To be addressed by the marketing authorisation holders for methadone medicinal products for oral use containing povidone

Article 107i of Directive 2001/83/EC

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

INN/active substances: methadone

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The marketing authorisation holders (MAHs) for methadone medicinal products for oral use containing povidone are requested to address the questions below:

Question 1

Concerning your methadone medicinal products for oral use containing povidone available in the EU/EEA, please provide:

a) Figures on patient exposure in EU/EEA since marketing, and if possible, by country and per year.

b) Any information or estimates of the extent of misuse by injection in the EU/EEA.

c) Information on the molecular weight (grade, e.g. K30, K90) and amount of povidone contained in your product.

Question 2

a) Please provide a cumulative review of all Individual Case Safety Reports (ICSRs) related to use by injection, of your product. Narratives and causality assessment should be included.

b) Please provide data from any other sources on fatal or serious cases related to injection of your product. Causality assessments should also be provided.

c) Please provide any evidence linking the injection of your particular product with the adverse drug reactions (including death, renal injury, lymphadenopathy, abdominal pain, liver disorder or weight loss) which may be associated with povidone deposits.

d) Please provide a discussion on plausible pathophysiological mechanisms by which povidone would be associated with the above referred risks.

Question 3

a) Please provide any additional data, published or unpublished, on the above mentioned risks in humans caused by or suspected to be caused by intravenously administered povidone with different molecular weight.

b) Please provide a review of relevant non-clinical data (pharmacokinetic and toxicological) and clinical data for intravenous administration of povidone including information on distribution and elimination of different molecular weight of povidone.

c) Please provide information on the physical and chemical changes and any hypothesis that such changes would be expected on the methadone product containing povidone upon heating.

Question 4

a) Please provide a justification for the utilisation of povidone in your methadone product.

b) Based on this and on the above mentioned potential risks associated with the injection of povidone of high molecular weight, please discuss the balance of utility and risks of povidone contained in your product and how the use of povidone in your product impacts on its overall benefit/risk balance.

Question 5

a) Please provide an overview of the risk minimisation measures (RMMs) currently in place to mitigate the potential risk of misuse of your product (by injection), including how it is reflected in the current product information.

b) Please provide proposals and justifications for any additional risk minimisation measures which may improve the benefit-risk balance of your product and prevent its misuse by injection. Please also comment on how the effectiveness of such measures should be monitored and assessed.

c) Please discuss the feasibility of performing a study to better understand the possible contribution of povidone in methadone products to fatal outcome, for example by collecting data on fatal cases that might be available in national forensic medicine authorities or organisations.