Summary of Risk Management Plan (RMP) for Cystadane (betaine anhydrous)

This is a summary of the RMP for Cystadane. The RMP details important risks of Cystadane, how these risks can be minimised, and how more information will be obtained about Cystadane's risks and uncertainties (missing information).

Cystadane's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Cystadane should be used.

This summary of the RMP for Cystadane should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report. Important new concerns or changes to the current ones will be included in updates of Cystadane's RMP.

I. The Medicine and What it is Used For

Cystadane is authorised for adjunctive treatment of homocystinuria, involving deficiencies or defects in cystathionine beta-synthase, cobalamin cofactor metabolism or 5,10-methylene-tetrahydrofolate reductase (see SmPC for the full indication). It contains betaine anhydrous as the active substance and it is administered orally.

Further information about the evaluation of Cystadane's benefits can be found in the Cystadane European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/cystadane.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cystadane, together with measures to minimise such risks and the proposed studies for learning more about Cystadane's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

Information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of important risks and missing information

Important risks of Cystadane are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important

risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cystadane. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

No important risks or missing information are included in the list of safety concerns for Cystadane.

Cerebral oedema was previously considered as an important identified risk for Cystadane. The risk of cerebral (brain) oedema has been included in the Product Information since the European launch date (15 February 2007). The frequency for the occurrence of cerebral oedema is considered to be uncommon with Cystadane. It is considered to be a known risk that requires no further characterisation and can be followed up via routine pharmacovigilance namely signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers. Therefore, cerebral oedema was removed from the list of safety concerns for Cystadane.

Interstitial lung disease was previously considered as an important potential risk for Cystadane. However, due to a lack of case reports that indicate a causal role of Cystadane, and considering that idiopathic pulmonary fibrosis is by definition not drug-induced interstitial lung disease, this risk was removed from the list of safety concerns for Cystadane.

In addition, use in pregnancy and lactation was considered as missing information for Cystadane. Data on a limited number of exposed pregnancies has not provided any significant safety data for the use of Cystadane during pregnancy or pertaining to the health of the foetus/newborn child. To date, no relevant epidemiologic data are available that indicate potential harm following the use of Cystadane in this patient population. Overall, it is considered that to date, there is no evidence to suggest that the product's safety profile would be expected to be different in this patient population; therefore, use in pregnancy and lactation was also removed from the list of safety concerns for the product. Section 4.6 of the SmPC for Cystadane sufficiently advises that during pregnancy, administering betaine anhydrous in addition to pyridoxine, folate, anticoagulant and diet under close monitoring of plasma homocysteine would be compatible with good maternal and foetal outcomes; however, Cystadane should not be used during pregnancy unless clearly necessary. It is also noted that because of lack of data, caution should be exercised when prescribing Cystadane to breast-feeding women.

II.B. Summary of Important Risks

The safety information in the Product Information is aligned to the reference medicinal product.

II.C. Post-authorisation Development Plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or a specific obligation of Cystadane.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Cystadane.