24 February 2022
EMA/203554/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Amversio

International non-proprietary name: betaine anhydrous

Procedure No. EMEA/H/C/005637/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Administrative information

| | |
|---|---|
| **Name of the medicinal product:** | Amversio |
| **Applicant:** | SERB SA<br>480 Avenue Louise<br>1050 Brussels<br>BELGIUM |
| **Active substance:** | Betaine |
| **International Non proprietary Name/Common Name:** | betaine anhydrous |
| **Pharmaco-therapeutic group (ATC Code):** | OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS, Amino acids and derivatives<br>(A16AA06) |
| **Therapeutic indication(s):** | Amversio is indicated as adjunctive treatment of homocystinuria, involving deficiencies or defects in:<br>• cystathionine beta-synthase (CBS),<br>• 5,10-methylene-tetrahydrofolate reductase (MTHFR),<br>• cobalamin cofactor metabolism (cbl).<br><br>Amversio should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet. |
| **Pharmaceutical form(s):** | Oral powder |
| **Strength(s):** | 1 g |
| **Route(s) of administration:** | Oral use |
| **Packaging:** | bottle (HDPE) |
| **Package size(s):** | 1 bottle + 3 measuring spoons (1g, 150mg, 100mg) |

# Table of contents

# List of abbreviations

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|---|---|
| CHMP | Committee for Medicinal Products for Human Use |
| EC | European Commission |
| ERA | Environmental Risk Assessment |
| FT-IR | Fourrier Transform Infrared Spectroscopy |
| GF-AAS | Graphite furnace atomic absorption |
| HDPE | High Density Polyethylene |
| HPLC | High performance liquid chromatography |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IP-MS | Inductively coupled plasma mass spectrometry |
| ICP-OES | Inductively coupled plasma atomic emission spectroscopy |
| Ph. Eur. | European Pharmacopoeia |
| TMA | Trimethylamine |
| SmPC | Summary of Product Characteristics |
| BE | Bioequivalence |
| MAA | Marketing Authorisation Application |
| CBS | cystathionine beta-synthase |
| MTHFR | 5,10 methylene tetrahydrofolate reductase |
| cbl | cobalamin cofactor metabolism |
| EURD list | the list of Union reference dates |
| RMP | Risk Management Plan |
| MAH | Marketing Authorisation Holder |
| PRAC | Pharmacovigilance Risk Assessment Committee |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant SERB SA submitted on 9 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Amversio, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Amversio is indicated as adjunctive treatment of homocystinuria, involving deficiencies or defects in:
- cystathionine beta-synthase (CBS),
- 5,10-methylene-tetrahydrofolate reductase (MTHFR),
- cobalamin cofactor metabolism (cbl).

Amversio should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Cystadane instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Cystadane 1 g Oral Powder
- Marketing authorisation holder: Recordati Rare Diseases
- Date of authorisation: 15-02-2007
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/06/379/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Cystadane 1 g Oral Powder
- Marketing authorisation holder: Recordati Rare Diseases
- Date of authorisation: 15-02-2007
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/379/001

## *1.3. Information on paediatric requirements*

Not applicable

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *1.5. Scientific advice*

The applicant did not seek Scientific advice from the CHMP.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Tomas Radimersky

The Rapporteur appointed by the PRAC was:

Rapporteur: Martin Huber

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| The application was received by the EMA on | 9 November 2020 |
| The procedure started on | 24 December 2020 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 11 March 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 29 March 2021 |
| The PRAC Rapporteur's updated Assessment Report was circulated to all | 9 April 2021 |

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| PRAC and CHMP members on | |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 22 April 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 18 October 2021 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on | 22 November 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 2 December 2021 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 16 December 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on | 21 January 2022 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 8 February 2022 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Amversio on | 24 February 2022 |

# 2. Scientific discussion

## *2.1. Introduction*

This centralised application for a marketing authorisation concerns a generic application according to article 10(1) of Directive 2001/83/EC for Amversio (betaine anhydrous), 1 g, oral powder. Application has been initially submitted by the Applicant Veriton Pharma Limited, UK.

Subsequently, the Applicant has been changed to. Serb, Brussels, Belgium in order to fulfil EU legal requirements.

The reference medicinal product is Cystadane 1 g oral powder (MAA No: EU/1/06/379/001, Recordati Rare Diseases, France). On 9 July 2001, orphan designation (EU/3/01/045) was granted by the European Commission to Orphan Europe, France, for betaine anhydrous for the treatment of homocystinuria. Betaine anhydrous has been authorised in the EU as Cystadane since 15 February 2007. Cystadane was withdrawn from the Community Register of designated orphan medicinal products in February 2017 at the end of the 10-years period of market exclusivity. Amversio has the same therapeutic indications as Cystadane, same qualitative and quantitative composition, same pharmaceutical form, strength and route of administration. This formulation is without any excipients.

No bioequivalence study between Amversio and the reference medicinal product Cystadane has been performed. As Amversio contains betaine only, with no excipients, and as betaine is also freely soluble in water, the 'oral solutions' section of Appendix II of the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**) applies.

**Proposed indication**

Amversio is indicated as adjunctive treatment of homocystinuria, involving deficiencies or defects in:

- cystathionine beta-synthase (CBS),
- 5,10 methylene tetrahydrofolate reductase (MTHFR),
- cobalamin cofactor metabolism (cbl).

Amversio should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.

Posology

Amversio treatment should be supervised by a physician experienced in the treatment of patients with homocystinuria.

*Children and adults*

The recommended total daily dose is 100 mg/kg/day given in 2 doses daily. However, the dose should be individually titrated according to plasma levels of homocysteine and methionine. In some patients doses above 200 mg/ kg/day were needed to reach therapeutic goals. Caution should be exercised with up titrating doses for patients with CBS deficiency due to the risk for hypermethioninaemia. Methionine levels should be closely monitored in these patients.

*Special populations*

*Hepatic or renal impairment*

Experience with betaine anhydrous therapy in patients with renal insufficiency or non-alcoholic hepatic steatosis has demonstrated no need to adapt the dose regimen of Amversio.

*Paediatric population*

Currently available data are described in section 5.1.

Method of administration

The bottle should be lightly shaken before opening. Three measuring spoons are provided which dispense either 100 mg, 150 mg or 1 g of betaine anhydrous. It is recommended that a heaped measuring spoon is removed from the bottle and a flat surface e.g. base of a knife is drawn across the top of the measure. This

will give the following doses: the green measuring spoon dispenses 100 mg, the blue measuring spoon dispenses 150 mg and the purple measuring spoon dispenses 1 g of betaine anhydrous.

The powder should be mixed with water, juice, milk, formula or food until completely dissolved and ingested immediately after mixing.

*Therapeutic monitoring*

The aim of treatment is to keep plasma levels of total homocysteine below 15 µmol/L or as low as possible. The steady state response usually occurs within a month.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as oral powder containing 1 g of betaine anhydrousas active substance.

No excipients are included in the finished product.

The product is available in white opaque HDPE bottles with a child resistant polypropylene cap with an induction seal liner as described in section 6.5 of the SmPC.

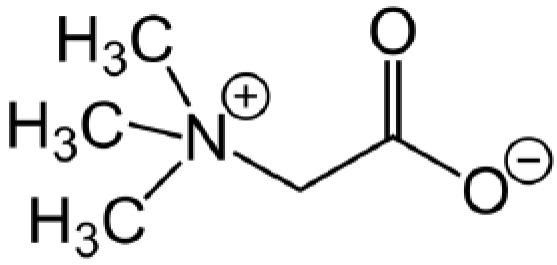
Each pack contains 1 bottle and three measuring spoons. The green measuring spoon dispenses 100 mg, the blue measuring spoon dispenses 150 mg, and the purple measuring spoon dispenses 1 g.

### 2.2.2. Active substance

***General information***

The chemical name of the active substance is N-trimethylglycine corresponding to the molecular formula $C_5H_{11}NO_2$. It has a relative molecular weight of 117.15 g/mol and the following structure:

**Figure 1: Active substance structure**




The chemical structure of the active substance was elucidated by a combination of infra-red-(IR)-analysis, NMR *(*$^1$H NMR, $^{13}$C NMR*)*, MS, and elemental analysis.

The active substance is a very hygroscopic white crystals or white crystalline powder freely soluble in water.

The active substance has a non - chiral molecular structure.

Polymorphism has not been observed for the active substance.

### *Manufacture, characterisation and process controls*

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Betaine (anhydrous) is manufactured from technical grade betaine as the starting material. Betaine technical grade is extracted from sugar beet molasses.

Justification for starting material designation based on ICHQ11 was provided in the restricted part of the ASMF. The CHMP agreed with the justification and the proposed starting material "technical grade betaine" was accepted.

Betaine anhydrous is synthesized in 12 main steps using commercially available well defined starting materials with acceptable specifications.

Critical steps in the manufacturing process were identified by a risk analysis (following the hazard analysis and critical control parameters (HACCP)-system) and they are documented, monitored and controlled. The proposed limits for the respective in-process controls are acceptable.

In humans, betaine is a metabolite formed in the body from the well-described and known choline metabolism. The degradation pathways include a couple of demethylation steps to glycine.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in two bags, the inner polyethylene bag is closed with a clip, the outer laminated aluminium foil bag is heat-sealed, and both bags are protected by a fibre drum. In between the inner and outer bag some desiccant material is placed. Conformity with EC 10/2011 as amended has been confirmed for the inner layer bag.

### *Specification*

The active substance specification includes tests for appearance (visual), odour (organoleptic), identification (FTIR), transmittance (UV/VIS), pH (Ph. Eur.), chlorides (Ph. Eur.), sulphates (Ph. Eur.), ammonium (colour reaction), iron (photometric detention), heavy metals (Colorimetry), arsenic (Ph. Eur.), amino acid analysis (Ph. Eur.), sugar impurities (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Titration), total viable aerobic count (Ph. Eur.).

Possible impurities from the starting materials could be some included amino acids or sugar residues. Accompanying amino acids are determined by using a specific method for eninhydrin positive substances with

post column derivatisation. The levels are in accordance with the European Pharmacopeia requirements and the ICHQ3A and it is considered satisfactory. Absence of sugar residues has been verified.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

***Stability***

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and other 3 commercial batched stored for up 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, odour, lost on drying, assay, transmittance, impurities, and total viable aerobic count. The analytical methods used were the same as for release and were stability indicating.All tested parameters were within the specifications

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container with restriction "Store in dry and dark in well closed drums."

## 2.2.3. Finished medicinal product

***Description of the product and pharmaceutical development***

The finished product is presented as white crystalline free flowing powder. The qualitative and quantitative composition is shown in Table 2.

**Table 1: Composition of finished product**

| Ingredient | Quantity (g) | %w/w | Function | Reference |
|---|---|---|---|---|
| Betaine Anhydrous | 180g | 100% | Active ingredient | In-house |

The purpose of the product development was to produce a generic medicinal product Betaine anhydrous 1g oral powder, taking Cystadane as the reference product.

Betaine anhydrous is known to be hygroscopic but remains free flowing when the moisture content is controlled.

The active substance exists as three forms: anhydrous, monohydrate and hydrochloride. The anhydrous form was selected due to the better organoleptic properties in comparison to monohydrate and hydrochloride salts. Betaine in anhydrous form is a white crystalline powder. It is freely soluble in water.

The finished product comprises the active substance only without the addition of any excipients.

Betaine anhydrous is moisture sensitive. The physical proprieties of the product may change with high temperature and moisture.

Amversio and Cystadane are chemically identical and accordingly contain the same active substance. No bioequivalence study between Amversio, and the reference medicinal product Cystadane has been provided, nor is such a study required. As the finished product contains betaine anhydrous only, with no excipients, and as the active substance is also freely soluble in water, the 'oral solutions' section of Appendix II of the guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **) applies.

The manufacturing process is a simple filling process to fill the active substance into the primary packaging. Since the active substance is hygroscopic the product manufacturing is performed in a clean, humidity-controlled environment to avoid any moisture ingress during manufacturing. Initially the active substance is sieved in a humidity-controlled room. Sieving is performed to remove any agglomerates or lumps. Filling of powder is also conducted in a humidity-controlled environment. Weight checks are performed during filling. The containers are induction sealed with an induction sealer at the specified setting to ensure no gaps or damage to the seal. Each container is then capped with a child-resistant cap.

The primary packaging is white opaque HDPE bottles with a child resistant polypropylene cap with an induction seal liner, The material complies with Ph. Eur. and EC requirements.

The primary packaging is further packed into a secondary carton containing three polypropylene dosing spoons. The three dosing spoons (green, blue, purple) are designed to dispense 100mg (0.14 cc), 150mg (0.22 cc) and 1g (1.46 cc) powder dose, respectively. The three dosing spoons are CE marked.

***Manufacture of the product and process controls***

The manufacturing process consists of 3 main steps: manufacturing process simply comprises filling, capping and cartoning. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated in 3 batches at a 1/8th scale by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process at full scale will be validated prior to commercial manufacture since this is a standard manufacturing process, this is considered satisfactory. No critical steps were identified and there are no intermediates in the process The in-process controls are adequate for this type of manufacturing process.

***Product specification***

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), appearance of solution (visual), fill weight (gravimetry), identification odour of powder (organoleptic), identification (FTIR), pH (Ph. Eur.), assay (titration, HPLC), trimethylamine (GC), loss of drying (Ph. Eur.), uniformity of mass of delivered dose (Ph. Eur.), and microbiology (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 commercial scale batches using a validated ICP-MS, ICP-OES and GF-AAS methods was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing,

***Stability of the product***

Stability data from 3 pilot scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH and 30°C/65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. All containers were stored in an upright position during stability.

Samples were tested for appearance of the finished product, appearance of a constituted solution, odour of powder, identification, pH, transmittance, loss on drying, assay, related substances, amino acids and residual saccharides, and microbiology. The analytical procedures used are stability indicating.

Product's moisture content continues to remain below the limit of ≤2.0%. Assay remains within the specification range. Also, the related substance trimethylamine was not detected at any time point for all storage conditions. Trending suggests all parameters will remain within specification at 36 months.

The finished product was tested for any change in quality of the product once the container was opened, the induction seal removed, and the polypropylene lid placed securely back onto the container. Two batches of Betaine were tested at 25ºC/60%RH. The rationale for this study was to establish the shelf- life of the product once the bottle is opened and induction seal removed. This study was performed for 6 months. All stability test parameters were within the agreed limits up to 3 months' time point. At the 6-month time point, all parameters except loss on drying were well within limits. Therefore, once opened the finished product has a shelf life of 3 months.

In-use stability reflecting the daily use were performed for 30 days on batches of the finished product under ambient temperature and high humidity conditions (75 % RH). The results were within the proposed specifications. Therefore, an in-use shelf life of 30 days can be assigned to the product. Additional results of stability testing performed on two batches of the finished product, in aqueous solution and in simulated gastric fluid were presented. Satisfactory assay results were provided for product solutions over 24 h in water and 2 h in simulated gastric fluid. Therefore, the finished product was shown to be stable in aqueous solution and simulated gastric fluid justifying use of constituted solution on day of preparation and no anticipated changes to the product on ingestion are expected.

Based on available stability data, the proposed shelf-life of the unopened bottle is 3 years, once the bottle is first opened the proposed shelf-life is 3 months and keep the bottle tightly closed in order to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. One issue was raised by CHMP as Major Objections (MO). The MO was related to redefinition of starting material. The issue was resolved satisfactorily by the applicant as described above.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6. Recommendation(s) for future quality development

Not applicable

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

### 2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Amversio, a naturally occurring compound, manufactured by SERB SA is considered unlikely to result in any significant increase in the combined sales volumes for all betaine anhydrous containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

### 2.3.3. Conclusion on the non-clinical aspects

The CHMP considers the justifications for absence of new non-clinical and ERA data as acceptable considering the type of application (natural occurring substance).

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This is an application for an oral powder containing betaine anhydrous 1g. To support the marketing authorisation application the applicant submitted an exemption to perform a bioequivalence study with the reference medicinal product, Cystadane.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

***Exemption***

No bioequivalence study between Amversio and the reference product Cystadane has been provided. As Amversio contains betaine only, with no excipients, and as betaine is also freely soluble in water, the 'oral solutions' section of Appendix II of the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) applies. This section states that: "If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived."

### 2.4.2. Conclusions on clinical aspects

The CHMP considered that the relevant criteria were met for Amversio to support the above exemption.

## *2.5. Risk Management Plan*

### 2.5.1. Safety concerns

None.

### 2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

### 2.5.3. Risk minimisation measures

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

No additional risk minimisation measures.

### 2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1 is acceptable.

### 2.5.5. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.5.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Product information*

### 2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# 3. Benefit-risk balance

This application concerns a generic version of betaine anhydrous as oral powder. The reference product Cystadane 1 g oral powder is indicated for the treatment of homocystinuria. No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

No bioequivalence study between Amversio and the reference medicinal product Cystadane has been performed. As Amversio contains betaine only, with no excipients, and as betaine is also freely soluble in water, the 'oral solutions' section of Appendix II of the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**) applies. This section states that: "If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived."

The CHMP considered that the relevant criteria were met for Amversio to support the above exemption.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus/majority decision that the benefit-risk balance of Amversio is favourable in the following indication:

Amversio is indicated as adjunctive treatment of homocystinuria, involving deficiencies or defects in:
- cystathionine beta-synthase (CBS),
- 5,10-methylene-tetrahydrofolate reductase (MTHFR),
- cobalamin cofactor metabolism (cbl).

Amversio should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.