ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cystadane 1 g oral powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of powder contains 1 g of betaine anhydrous.
Three measuring spoons dispense 1 g, 150 mg and 100 mg of betaine anhydrous.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder
White free flowing powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

The recommended total daily dose in adult and paediatric patients over 10 years of age is 6 g per day administered orally in divided doses of 3 g two times per day. However, dose titration may be preferable in paediatric patients.

In paediatric patients less than 10 years of age, the usual effective dose regimen is 100 mg/kg/day given in 2 doses daily; increasing the frequency above twice daily and/or the dose above 150 mg/kg/day does not improve the homocysteine-lowering effect.

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

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 container and a flat surface e.g. base of a knife is drawn across the top of the measure. This will give the following doses: small measure 100 mg, middle size measure 150 mg and large measure 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 µM or as low as possible. The steady-state response usually occurs within a month.

4.3 Contraindications

Hypersensitivity to betaine.

4.4 Special warnings and precautions for use

Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting betaine therapy (see section 4.8). Complete recovery was seen after treatment discontinuation:

- Plasma methionine level should be monitored, at start of treatment and periodically thereafter. The plasma methionine concentrations should be kept below 1000 µM.
- If any symptoms of cerebral oedema like morning headaches with vomiting and/or visual changes appear, plasma methionine level and compliance to the diet should be checked and treatment with Cystadane interrupted.
- If symptoms of cerebral oedema recur after re-introduction of treatment then betaine therapy should be discontinued indefinitely.

To minimize the risk of potential drug interactions, it is advisable to leave 30 minutes between the intake of betaine and amino acids mixtures and/or medicinal products containing vigabatrin and GABA analogues (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Based on *in vitro* data, betaine might interact with amino acids mixtures and medicinal products containing vigabatrin and GABA analogues.

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number (7) of exposed pregnancies indicate no adverse event of betaine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiologic data are available. Animal reproduction studies have not been conducted. During pregnancy, administering betaine in addition to pyridoxine, folate, anticoagulant and diet under close monitoring of plasma homosysteine would be compatible with good maternal and foetal outcomes. **However**, Cystadane should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is not known whether betaine is excreted in human milk (although its metabolic precursor, choline, occurs at high levels in human milk). Because of lack of data, caution should be exercised when prescribing Cystadane to breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Experience derived from exposure to betaine in about 1,000 patients.

Reported adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as*:* very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders	Uncommon: anorexia
Psychiatric disorders	Uncommon: agitation, depression, irritability, personality disorder, sleep disturbed
Nervous system disorders	Uncommon: brain oedema*
Gastrointestinal disorders	Uncommon: dental disorders, diarrhoea, glossitis, nausea, stomach discomfort, vomiting
Skin and subcutaneous tissue disorders	Uncommon: hair loss, hives, skin odour abnormal
Renal and urinary disorder	Uncommon: urinary incontinence
Investigations	Very common: blood methionine increased*

*Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting betaine therapy, with complete recovery after treatment discontinuation. High increases in plasma methionine levels in a range from 1,000 to 3,000 µM were noted in these patients. As cerebral oedema has also been reported in patients with hypermethioninemia, secondary hypermethioninemia due to betaine therapy has been postulated as a possible mechanism of action. For specific recommendations, refer to section 4.4.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism product, ATC code: A16A A06.

Betaine was shown to lower plasma homocysteine levels in the three types of homocystinuria, i.e. CBS deficiency; MTHFR deficiency and cbl defect. The extent of this effect was dependent on the absolute degree of hyperhomocysteinemia, being higher in severe hyperhomocysteinemia.

Betaine acts as a methyl group donor in the remethylation of homocysteine to methionine in patients with homocystinuria. As a result, plasma levels of homocysteine should decrease in these patients, to 20-30 % of pre-treatment levels.

Elevated homocysteine plasma levels are associated with cardiovascular events such as thrombosis, osteoporosis, skeletal abnormalities, and optic lens dislocation. In observational studies, clinical improvement (cardiovascular and neurodevelopmental) was reported by the treating physician in about 75% of patients taking betaine. Most of these patients were also receiving other treatments such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin) and folate with variable biochemical responses. In most cases, adding betaine resulted in a further reduction in plasma homocysteine level. It is likely that due to the multiple nature of therapy (dietary, pharmaceutical, supportive) in these patients, there may be an element of overestimation in the clinical effects of betaine treatment. Late detection of homocystinuria in symptomatic state is responsible for residual morbidity due to irreversible damage to connective tissue (ophtalmological, skeletal) that can not be corrected by further therapy. The available clinical data do not allow correlating posology and clinical efficacy. There is no evidence of development of tolerance.

Betaine has also been shown to increase plasma methionine and S-adenosyl methionine (SAM) levels in patients with MTHFR deficiency and cbl defects. In CBS-deficient patients without dietary restriction of methionine, excessive accumulation of methionine has been observed. In a few cases, increased plasma methionine levels were associated with cerebral oedema (see sections 4.4 and 4.8).

Monitoring plasma homocysteine levels has demonstrated that the onset of action of betaine occurred within several days and that a steady-state response was achieved within one month.

In paediatric patients less than 3 years of age, the usual effective dose regimen is 100 mg/kg/day given in 2 doses daily; increasing the frequency above twice daily and/or the dose above 150 mg/kg/day does not improve the homocysteine-lowering effect.

Betaine supplementation was shown to improve the metabolic abnormalities in the cerebrospinal fluid of patients with homocystinuria.

Monitoring betaine plasma concentrations does not help to define the efficacy of treatment, since these concentrations do not directly correspond to the flux through the cytosolic betaine homocysteine methyl transferase pathway.

5.2 Pharmacokinetic properties

The absolute bioavailability of betaine has not been determined. In healthy adult volunteers (age between 21 to 49 years), after a single oral dose of betaine (50 mg/kg), absorption was rapid (t_{max} = 0.9 ± 0.3 hours and a C_{max} = 0.9 ± 0.2 mM). Betaine was rapidly distributed into a relatively large volume (V/F = 1.3 l/kg), with a slow elimination rate (mean half life = 14 h, mean total body clearance, CL/F, = 84 ml/h/kg), renal clearance being negligible (5% of total body clearance), assuming 100% bioavailability. After a repeated dose regimen of 100 mg/kg/day for 5 days, the absorption kinetics did not change but the distribution half life was prolonged significantly (up to 36 h), indicating saturable transport and redistribution processes.

The pharmacokinetic data of homocystinuric patients on long-term betaine supplementation are very similar to those of healthy volunteers. This demonstrates that differences in betaine kinetics are most probably due to betaine depletion in untreated homocystinuria and are only meaningful for the initial treatment.

5.3 Preclinical safety data

At high doses, a CNS depressant effect and irritation of the gastrointestinal tract was seen in rats. Long-term carcinogenicity and reproductive toxicity studies have not been conducted on betaine. A standard battery of genotoxicity test reveals no specific hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 2 years

After the first opening: 1 month.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with a child resistant closure.
Each pack contains 1 bottle with 180 g of powder.
Three measuring spoons are included in each pack.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orphan Europe SARL
Immeuble “Le Guillaumet”
F - 92046 Paris-La Défense
France

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Orphan Europe S.A.R.L.
Immeuble "Le Guillaumet"
F-92046 Paris La Défense
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

The Marketing Authorisation Holder commits to performing the studies as detailed in the Pharmacovigilance Plan.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cystadane 1 g oral powder
Betaine anhydrous

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of powder contains 1 g of betaine anhydrous.
Three measuring spoons dispense 1 g, 150 mg and 100 mg of betaine anhydrous.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

180 g of oral powder and three measuring spoons.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Lightly shake the bottle before opening.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}
Shelf life after the first opening: 1 month.
Opened:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orphan Europe SARL
Immeuble “Le Guillaumet”
F - 92046 Paris-La Défense
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystadane 1 g oral powder

PARTICULARS TO APPEAR ON THE THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Cystadane 1 g oral powder
Betaine anhydrous

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of powder contains 1 g of betaine anhydrous.
Three measuring spoons dispense 1 g, 150 mg and 100 mg of betaine anhydrous.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

180 g of oral powder.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Lightly shake the bottle before opening.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}
Shelf life after the first opening: 1 month.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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France

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cystadane 1 g oral powder

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cystadane 1 g oral powder
Betaine anhydrous

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Cystadane is and what it is used for
2. Before you take Cystadane
3. How to take Cystadane
4. Possible side effects
5 How to store Cystadane
6. Further information

1. WHAT CYSTADANE IS AND WHAT IT IS USED FOR

Cystadane contains betaine anhydrous which is intended to be an adjunctive treatment of homocystinuria, an inborn error of metabolism.

Methionine is an amino acid which is present in regular food protein (e.g. meat, fish, milk, cheese, eggs). It is converted into homocysteine which is then normally converted into cysteine during digestion. Homocystinuria is a disease caused by the accumulation of homocysteine which is not converted to cysteine and is characterized by formation of clots in the veins, bone weakness, and skeletal and crystalline lens abnormalities. The use of Cystadane together with other treatments such as vitamin B6, vitamin B12, folate and a specific diet aims to reduce the elevated homocysteine levels in your body.

2. BEFORE YOU TAKE CYSTADANE

Do not take Cystadane
If you or your child are allergic (hypersensitive) to betaine.

Take special care with Cystadane
If you notice side effects like headaches, vomiting or a change in your vision, please contact your doctor immediately, they could be signs of a brain oedema. In that case your doctor will monitor your methionine level in your body and may review your diet. Your treatment with betaine may need to be interrupted.
If you are treated with Cystadane and with an amino-acid mixture and if you need to take other medicines at the same time, leave 30 minutes between the intake (see “taking other medicines”).

Taking other medicines
If you are taking amino-acid mixture or medicines such as vigabatrin or Gaba analogues, please tell your doctor as they might interact with your treatment with betaine.
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Please inform your doctor if you are pregnant or breast-feeding. Your doctor will decide if the medicine may be used during pregnancy and breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.

3. HOW TO TAKE CYSTADANE

Always take Cystadane exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The daily dose in adults, adolescents and children over 10 years of age is 6 g per day divided in 2 doses of 3 g per day.
In children less than 10 years of age, the daily dose will be calculated from the child's body weight by your doctor.
You or your child will therefore need regular blood tests to determine the correct daily dose.
The use of this medicine will be supervised by a physician experienced in the treatment of patients with homocystinuria.

Cystadane should be taken orally (by mouth).
To measure the dose:
- shake the bottle lightly before opening
- take the correct measuring spoon:
  - the small spoon measures 100 mg of betaine anhydrous powder;
  - the middle size spoon measures 150 mg of betaine anhydrous powder ;
  - the large spoon measures 1 g of betaine anhydrous powder.
- take a heaped spoonful of powder out of the bottle
- pass the flat back of a knife over the top of the spoon
- the powder left in the spoon is one spoonful
- take the correct number of spoonfuls of powder from the bottle

Mix the measured dose of powder with water, juice, milk, formula or food until completely dissolved and ingest immediately after mixing.

If you forget to take Cystadane:
Do not take a double dose to make up for forgotten doses.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cystadane can cause side effects, although not everybody gets them.

The following side effects were reported as follows: very common (more than 1 out of 10 persons), common (more than 1 out of 100 persons and less than 1 out of 10 persons), uncommon (more than 1 out of 1,000 persons and less than 1 out of 100 persons), rare (more than 1 out of 10,000 persons and less than 1 out of 1,000 persons), very rare (less than 1 out of 10,000 persons).

Very common: blood methionine increased.

Uncommon: decreased appetite, agitation, depression, irritability, personality disorder, sleep disturbance, oedema of the brain (see heading "Take special care with Cystadane" in section 2), dental disorders, diarrhoea, inflammation of the tongue, nausea, stomach discomfort, vomiting, hair loss, hives, skin odour abnormality and urinary incontinence.

Since some of these side effects are serious, ask your doctor to explain their warning signs.

If any of the side effects gets serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CYSTADANE

Keep out of the reach and sight of children

Do not use Cystadane after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.
After the first opening of the bottle, the product should be used within 1 month.

Medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Cystadane contains
- The active substance is betaine anhydrous. 1 g of oral powder contains 1 g of betaine anhydrous. Three measuring spoons dispense 1 g, 150 mg and 100 mg of betaine anhydrous.
- There is no other ingredient.

What Cystadane looks like and contents of the pack
Cystadane is a white crystalline oral powder. It is presented in bottles with child resistant closures. Each bottle contains 180 g of betaine anhydrous powder. Three measuring spoons are enclosed in the carton to assist you in measuring out the dose prescribed by your doctor.

Marketing Authorisation Holder and Manufacturer
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/. There are also links to other websites about rare diseases and treatments.