

CYSTADANE® 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 homocysteine 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 ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), 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 (ophthalmological, 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 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.

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 ($t_{\max} = 0.9 \pm 0.3$ hours and a $C_{\max} = 0.9 \pm 0.2$ 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: 3 years

After the first opening: 3 months.

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 Wilson"
70 Avenue du General de Gaulle
F-92 800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/379/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2007

10. DATE OF REVISION OF THE TEXT