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.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral powder.
White crystalline 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.

Posology

Children and Adult

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 Cystadane.

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: 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 the active substance.

4.4 Special warnings and precautions for use

Uncommon cases of severe cerebral oedema associated with hypermethioninemia were reported with betaine anhydrous therapy in patients with CBS deficiency (see section 4.8). Complete recovery was seen after treatment discontinuation:

- *The plasma methionine concentrations should be kept below 1000 µM. It is recommended to measure plasma methionine level at start of treatment and about annually or biannually thereafter. If methionine increases particularly above the first safety threshold of 700 µmol/L, patient should be monitored more frequently and compliance with diet should be checked. In order to reduce methionine levels, modification of diet as well as dose reduction of Cystadane or temporal interruption of Cystadane treatment should be considered.*
- 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 anhydrous therapy should be discontinued indefinitely.

To minimise the risk of potential drug interactions, it is advisable to leave 30 minutes between the intake of betaine anhydrous 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 anhydrous might interact with amino acids mixtures and medicinal products containing vigabatrin and GABA analogues.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse event of betaine anhydrous 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 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.

Breast-feeding

It is not known whether betaine anhydrous 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.

Fertility
No data is available.

4.7 Effects on ability to drive and use machines

Cystadane has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In general, adverse reactions seen with betaine anhydrous therapy appeared to be not serious and are mainly related to the gastrointestinal system. Gastrointestinal disorders like diarrhoea, glossitis, nausea, stomach discomfort, vomiting and dental disorders may occur uncommonly.
The most commonly reported adverse reaction during treatment is blood methionine increased. Complete recovery was seen after treatment discontinuation (see section 4.4).

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

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

	increased*

Description of selected adverse reactions
*Uncommon cases of severe cerebral oedema and hypermethioninemia were reported within 2 weeks to 6 months of starting betaine anhydrous therapy in patients with CBS deficiency, with complete recovery after treatment discontinuation.
Symptoms of cerebral oedema include morning headaches with vomiting and/or visual changes
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 anhydrous therapy has been postulated as a possible mechanism of action.
For specific recommendations, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, ATC code: A16AA06.

Mechanism of action
Betaine anhydrous 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.

Pharmacodynamic effects

Betaine anhydrous 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.

Betaine anhydrous 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.

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

Clinical efficacy and safety

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 anhydrous. 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 anhydrous 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 anhydrous treatment. Late detection of homocystinuria in symptomatic state is responsible for residual morbidity due to irreversible damage to connective tissue (ophtalmological, skeletal) that cannot 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.

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 anhydrous occurred within several days and that a steady-state-response was achieved within one month.

Paediatric population

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.

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

Absorption
The absolute bioavailability of betaine anhydrous has not been determined. In healthy adult volunteers (age between 21 to 49 years), after a single oral dose of betaine anhydrous (50 mg/kg), absorption was rapid (t_{max} = 0.9 ± 0.3 hours and a C_{max}-= 0.9 ± 0.2 mM).
After a repeated dose regimen of 100 mg/kg/day for 5 days, the absorption kinetics did not change.

Distribution
Betaine anhydrous was rapidly distributed into a relatively large volume (V/F = 1.3 l/kg).
After a repeated dose regiment of 100 mg/kg/day for 5 days, the distribution half life was prolonged significantly (up to 36 h), indicating saturable transport and redistribution processes.

Biotransformation
Betaine anhydrous is a methyl group donor

Elimination
With a slow elimination rate (mean half life-= 14 h, mean total body clearance, CL/F, = 84 ml/h/kg), renal clearance is negligible (5% of total body clearance), assuming 100% bioavailability.

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 anhydrous. 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.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottles with a child resistant closure.
Each pack contains 1 bottle with 180 g of powder and three measuring spoons.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Tour Hekla
52, Avenue du General de Gaulle
F-92 800 Puteaux
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15266/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

22/01/2025