SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cystagon. This scientific discussion has been updated until 1 October 2002. For information on changes after this date please refer to module 8B.

1. Introduction

Nephropathic cystinosis is a rare autosomal recessive disease. It is characterised by an accumulation of free cystine in the lysosomes (lysosomal storage disease) of various cell types and results in cystine crystals deposition in the kidney, brain, cornea, conjunctiva, bone marrow, lymphatic nodes, leukocytes and other organs. Diagnosis can be established by measuring cystine levels in white blood cells Children with this lethal disease develop end-stage kidney failure in a short period of time and usually enter into dialysis or transplant program by the end of the first decade of life.

Variant forms of cystinosis are also known including an intermediate form in which end-stage renal disease is reached somewhere in the second to third decade of life, and a benign variant in which the only systemic manifestation are photophobia and corneal crystals.

The treatment of cystinosis nephropathy involves replacement of fluid and electrolytes losses. Cysteamine is not available as a proprietary medicinal product in the European Union, but is already used in different forms (cysteamine hydrochloride, phosphocysteamine, cysteamine bitartrate) for the treatment of these patients.

Cystagon contains cysteamine bitartrate. Cysteamine bitartrate is the name currently used whereas the International Non-proprietary Name of the product is mercaptamine bitartrate.

2. Chemical, pharmaceutical and biological aspects

Cystagon is presented in white hard gelatin capsules containing 50 mg or 150 mg of cysteamine formulated as cysteamine bitartrate. The two different strengths are identified by the capsule size and by a specific printing (CYSTA 50 or CYSTA 150) on the capsule body.

Development pharmaceutics

The capsule formulation has been selected in order to improve treatment compliance (improved palatability compared to the sulfide-like odour of other cysteamine solutions). The second objective was to obtain a better stability compared to oral solutions. The excipients were selected in order to minimise the moisture content and therefore avoid bitartrate instability.

The formulation is empirical and only justified by the stability data.

Compatibility studies with the selected packaging were not provided but the selected packaging was considered acceptable on the basis of the stability studies. A desiccant unit containing black activated carbon and silica gel granules is included in the bottles.

A dry granulation technique was used because cysteamine bitartrate is hygroscopic and quickly oxidises in the presence of moisture.

Method of preparation of the drug product

The capsules are manufactured by a single blending/compacted milled process which lead to a cysteamine bitartrate intermediate used for encapsulation of both strengths. The manufacturing process is described for a 100 kg batch size of cysteamine bitartrate intermediate which is used for about 100 000 capsules of 50 mg and 130000 capsules of 150 mg. A diagram showing controls and specifications was enclosed for the preparation of the intermediate. The manufacturing process yields an intermediate bulk and a final product with acceptable physical and chemical characteristics.

The precautions taken to protect the active substance during the manufacturing process have been described. A clear validated procedure of the handling of the active substance during the manufacturing process should be provided.

Control of starting material

Active substance

The pharmaceutical documentation consists of an open documentation and a confidential dossier (DMF). An EDMF has been submitted to the EMEA by Profarmaco and a letter of access is presented in the documentation.

The synthetic pathway for cysteamine bitartrate is provided.

Cysteamine bitartrate is easily soluble in water. Its structure is supported by the results of elemental analysis and data from several spectroscopic techniques. Cysteamine base without the bitartrate moiety does not present isomerism.

The revised specifications including the colour specification, the tightening of ignition residue specification and a more stringent particle specification were considered acceptable. Specifications limits for cysteamine are 97 - 102%.

Results were presented for three batches manufactured. The proposed analytical controls were not able to confirm if all potential, product related and process related, impurities were adequately studied. Therefore cysteamine tartrate and bitartrate levels should be included in the specifications which already include the degradation product of cystamine. A new limit for single and total impurities was defined and will be reviewed according to the observed results by Gas Chromatography/ Mass Spectrometry.

The applicant has provided some information on the raw material used for manufacture of the active substance. However it is not possible to assess the impurity profile from raw materials before the impurities reports are submitted. One of the material, hydrochloride, can sometimes react with an thiol group to yield a chlorine derivative which is potentially toxic. This potential impurity should be searched and a limit should be proposed and justified.

Other components

Certificates of analysis issued by the manufacturer are presented for each of the excipients. The functional details of the excipients are described.

Packaging material

Diagrams and construction of the different bottles, closures and desiccant as well as their specifications and control methods are fully described. The certificates of analysis provided for each component give results which conform to specifications. The stability data for capsules stored in the defined primary packaging up to 2 years, and 30 months for some batches, demonstrate that those packs are entirely suitable for both dosage forms.

Control tests on intermediate product material

The cysteamine bitartrate bulk is prepared for both 50 mg and 150 mg encapsulation. Bulk density and sieve analysis are controlled on each batch production to check the reproducible homogeneity of the powder. The same assay content limits are applied for the bulk and capsules control at release.

The specification for the contents have been revised and tightened to 95 - 105%.

Control tests on the finished product

Specification used to control the quality is based on standard requirements for capsule dosage forms. All methods have been validated and the same limits are applied at manufacture and throughout the proposed shelf-life of the product for all test parameters.

The specifications at release for related substances and loss on drying were not supported by the results presented in the batch analysis and were therefore tightened. The specifications at release for content were adapted to meet the European guidelines (95 - 105%).

Information on 3 manufacturing batches (indicating the manufacturing scale) should be provided. It should be clearly established that the manufacturing process yields a finished product with a reproducible quality. Data on the microbiological quality of the finished product should be provided as well.

Stability

Stability of the active substance

Cysteamine contains a thiol group which is extremely susceptible to oxidation forming the corresponding disulphide cystamine which is the main degradation product. The speed of oxidation of thiols may increase through the effects of heat and light.

Results are presented from stability studies on five batches manufactured between June 1992 and January 1995 stored at room temperature (+27.2°C ± 2.5°C) up to 3 years. The batches were stored in containers simulating the packaging system. The analytical methods applied were the same as at release. The substance is hygroscopic and unstable under the studied storage conditions.

Preliminary results at 6 months on one batch stored at 15-30°C/40-60% relative humidity under closed conditions (produced in January 1996, batch size 140 kg) were enclosed. Data on three other batches will be submitted later in order to establish the storage conditions for the bulk product and the re-test period. For the time being the manufacturer should control each active substance batch immediately before using it in the manufacture of the finished product.

No data on degradation under stress conditions were provided. Results of studies regarding the intrinsic stability of the active substance will be provided later.

Stability of the finished product

Four batches of each strength manufactured on production scale were packed and stored in high-density polyethylene bottles of 100 and 500 capsules. The storage conditions are in conformity with European Union guideline requirements. The only change observed was a slight increase in cystamine level and in moisture but all results are within the specifications limits. The release limits have been corrected to 90 - 105%.

The trend for hygroscopy was confirmed and on the basis of the batches obtained during 1994, a shelf life of 2 years can be accepted.

3. Toxico-pharmacological aspects

The preclinical dossier refers mainly to old bibliographical data on cysteamine hydrochloride which are not up to current standards. No experimental toxicological and pharmacological studies were carried out by the applicant.

Pharmacodynamics

Review of cysteamine pharmacodynamics was made through a bibliographical research in four databases for the period 1980-1996.

There are no animal models of cystinosis to study the pharmacodynamic effects of cysteamine.

No data concerning general pharmacodynamics are available. Several well-known pharmacodynamic effects that could be relevant to the side-effects profile of the drug, such as the action on somatostatin, prolactin and glucagon and the induction of duodenal ulcers were described in rats.

Pharmacokinetics

No animal pharmacokinetic data are available.

Toxicology

Single dose toxicity

Although the documentation did not comply with standard toxicological methods and presented important deficiencies, the gastrointestinal tract could be considered as the main target organ as demonstrated in single dose toxicity studies in rodents. The test substance was cysteamine hydrochloride.

Repeated dose toxicity

Subacute toxicity was studied in a four-week oral study in 2 monkeys (150 mg/kg/day) and in a 13 week feeding study in rabbits (100 mg/kg/day). Chronic toxicity was only studied in 5 monkeys given 20-150 mg/kg/day orally for one year. No gastrointestinal effect was observed in these studies.

Although the low doses were below the therapeutic dosage (50-60 mg/kg/day of cysteamine bitartrate), the no-effect level could not be established.

Single and repeated administration to rats indicated that gastric and duodenal ulcers can be produced at high doses of 200 mg/kg and above by subcutaneous injection.

The chronic toxicity study in monkeys and another 9-week study in rabbits showed effects on bone marrow. However the available data neither demonstrate nor totally exclude the effect of cysteamine on bone marrow. This is addressed into the relevant parts of the Summaries of Product Characteristics.

Other studies in rats confirmed a potential for duodenal and gastric ulcerogenic effects, and cataract development with early administration of the study.

Reproduction toxicity

The reproduction toxicity data originate from old publications which do not follow current guidelines. Four studies with cysteamine bitartrate have been provided. But there is only one proper study in rats. The others are dose ranging studies (two in rats and one in rabbits) with no foetus examinations.

Maternotoxicity was observed at all doses tested. An embryolethal effect was reported from 100 mg/kg. Furthermore the dose ranging study in rabbit was not assessable because of a higher sensitivity of this species to cysteamine. No information is provided on foeto-placental transfer and on milk transfer.

There are not sufficient data available to assess the effects of cysteamine on reproduction function. The information in Sections 4.3 Contra-indications and 4.6 Pregnancy and Lactation addresses this situation.

Further to the Commission Decision issued on 23 June 1997, two new articles on the reproductive and embryo-foetal development safety of oral cysteamine (administered as phosphocysteamine) in the rat have been published. Cysteamine is shown to be teratogenic in rats at doses equal or greater than 100 mg/kg/day. This teratogenic dose is equivalent to 0.6 g /m^2/day in the rat, which is less than half the recommended clinical maintenance dose of cysteamine (1.30 g/m^2/day). Therefore, the Marketing Authorisation Holder submitted a Type II variation application on 7 November 2000 to update the relevant sections of the SPC to revise the information on pregnancy based on new preclinical data on the reproduction toxicity of the active substance.

Mutagenic potential

Genotoxicity studies were incomplete and did not comply with European Union guidelines. There was however *in vitro* evidence of a clastogenic potential of cysteamine. The applicant was therefore requested to complete genotoxicity studies.

The company provided the results of an AMES test and a Mouse Micronucleus test. These studies indicated that no mutations or micronuclei were induced at the dose levels studied. The results were considered satisfactory.

Carcinogenicity

No data are available.

Immunogenicity

No data are available.

Risk-benefit considerations for a potentially effective drug intended for a disease whose alternative is death at an early stage recommend the preclinical dossier to be accepted despite the deficiencies. The applicant has been requested to provide toxicological studies to determine the mutagenicity and genotoxicity

4. Clinical aspects

Cystinosis is a very rare disease and therefore a traditional clinical development program has not been performed owing to very small numbers of available patients.

Diagnosis can be established by cystine levels in white blood cells and expressed as nanomoles of hemicystine per milligram protein (as some analytical methods do not differentiate disulfide cystine

and thiol cystine). Normal individuals have white blood cell cystine levels of less than 0.2 whereas subjects heterozygous for cystinosis have levels below 1 nmol/hemicystine/mg protein. Individuals with nephropathic cystinosis have white blood cell levels of more than 2 nmol/hemicystine/mg protein.

White blood cell cystine levels below 1 nmol/hemicystine/mg protein have been chosen as the target level marker of drug efficacy measured 5 to 6 hours following administration of the drug. This level is approximately the upper level of cystine in heterozygotes. Since heterozygotes have no symptoms or signs of renal or other organ dysfunction, this level is compatible with normal renal function. Patients in whom those levels were not reached were considered to be inadequately treated.

The clinical documentation describes studies using cysteamine hydrochloride, phosphocysteamine and cysteamine bitartrate in different formulations. The capsule formulation may increase compliance by decreasing the unpleasant taste and smell of cysteamine. Cysteamine hydrochloride was the first formulation to be tried and was administered as a solution every 6 hours with an average maintenance dose of 50 mg/kg/day.

Clinical pharmacology

Pharmacodynamic studies

There is little information in the dossier regarding cysteamine pharmacodynamics. Orally administered cysteamine bitartrate rapidly dissociates in gastrointestinal tract into active cysteamine. Lysosomal cystine accumulation in cystinosis results from the defective transport of cystine across the lysosomal membrane into the cytoplasm. The cystine-depleting efficacy of cysteamine has been demonstrated *in vitro* and *in vivo*. It has been shown that cysteamine freely crosses the cytoplasmic membrane concentrating in the acidic lysosomes. There it reacts with cystine to form cysteine and cysteine-cysteamine mixed disulphide which leave cystinotic lysosomes.

Pharmacokinetic studies

There is a lack of pharmacokinetic data but a new kinetic study is planned. Its results will be submitted when available.

Absorption, distribution, metabolism and elimination studies have not been performed. Interaction data are also missing.

As most clinical efficacy studies have been carried out with cysteamine hydrochloride and phosphocysteamine, bioequivalence studies between these 2 formulations and cysteamine bitartrate were performed.

Study CYST 9301 and **study CYST 9929** were carried out in male healthy volunteers (8 and 24 respectively) randomly assigned to cysteamine bitartrate capsules or cysteamine hydrochloride solution corresponding for both formulations to 1050 mg cysteamine base). The 2 formulations were considered bioequivalent in these studies.

Study CYST 9235 was carried out in 8 patients with cystinosis already receiving cysteamine hydrochloride or phosphocysteamine solutions for at least 1 year. These patients were switched to equimolar (in terms of free base) doses of cysteamine bitartrate capsules and treated for 21 days.

Mean plasma cysteamine concentrations following treatment with cysteamine bitartrate capsules were higher than those following treatment with the solutions. The effect on white blood cells cystine of bitartrate capsules was approximately twice that of the solution.

Therefore both formulations cannot be considered equivalent in patients with cystinosis at steady state. Cysteamine bitartrate at the dose used induced a greater reduction in the white blood cells cystine levels below 1 nmol/hemicystine/mg protein.

Post-marketing data - Further to the Commission Decision issued on 23 June 1997 and as a part of a specific obligation, the study entitled "Estimation of oral cysteamine bitartrate pharmacokinetics at steady-state in cystinotic patients" was submitted on January 21st, 2000.

The results showed that the decrease in leucocyte cystine levels is correlated to the cysteamine plama concentration over the six hours following the administration of Cystagon. The leucocyte cystine level reaches its minimum (mean (± sd) value: 1.8 ± 0.8 hours) slightly later than the peak plasma

cysteamine concentration (mean (± sd) value: 1.4 ± 0.4 hours) and returns to its baseline level as the plasma cysteamine concentration decreases at 6 hours post-dose. Following a single oral dose of cysteamine bitartrate equivalent to 1.05 g of cysteamine free base in healthy volunteers, the mean (±sd) values for the time to peak and peak plasma concentration are 1.4 (±0.5) hours and 4.0 (±1.0) µg/ml, respectively. In patients at steady state, these values are 1.4 (± 0.4) hours and 2.6 (±0.9) µg /ml, respectively, after a dose ranging from 225 to 550 mg. The in vitro plasma protein binding of cysteamine, which is mostly to albumin, is independent of plasma drug concentration over the therapeutic range, with a mean (±sd) value of 54.1 % (±1.5). The plasma protein binding in patients at steady state is similar: 53.1% (±3.6) and 51.1% (±4.5) at 1.5 and 6 hours post-dosing, respectively.

In a pharmacokinetic study performed in 24 healthy volunteers for 24 hours, the mean estimate (±sd) for the terminal half-life of elimination was 4.8 (± 1.8 hours). The elimination of unchanged cysteamine in the urine has been shown to range between 0.3% and 1.7% of the total daily dose in four patients; the bulk of cysteamine is excreted as sulphate. Very limited data suggest that cysteamine pharmacokinetic parameters may not be significantly modified in patients with mild to moderate renal insufficiency. No information is available for patients with severe renal insufficiency.

On 7 November 2000, the Marketing Authorisation Holder submitted a Type II variation application to update the relevant sections of the SPC in order to incorporate the pharmacokinetic information obtained in this study.

Clinical experience

In the three studies presented, a total of 234 patients with nephropathic cystinosis have been treated over a 12-year period. Patients were diagnosed by increased levels of white blood cells cystine (> 0.2 nmol/hemicystine/mg protein), cystine crystals in cornea or in bone marrow. Mean age of diagnosis was 21 months whereas mean age of entry was 41 months.

Both the representativity of the population and inclusion criteria are appropriate. Efficacy criteria were maintenance of renal function (renal function and/or renal death was assessed by creatinine clearance levels, calculated renal clearance, need for dialysis or transplantation), improved survival, maintenance of growth velocity and levels of white blood cells cystine.

No formal double blind placebo controlled efficacy studies are available both for ethical reasons (positive initial results, lack of therapeutic alternative and fatal outcome of the disease) and practical reasons (odour and taste of cysteamine).

The dosages given were usually chosen with the aim to achieve a reduction of white blood cells cystine below 2 nmol/hemicystine/mg protein. Patients who did not achieve these low levels were considered to have been inadequately treated.

Efficacy

Three clinical studies for efficacy are available. An initial open study with historical placebo treated controls (9148-1), a retrospective study (9148-2) in which many of the patients were probably undertreated and an extension of 9148-1 including also some newly recruited patients (9148-3) in which two different doses were studied.

Study 9148-1 was an open and multicentre study which enrolled 97 patients (males 22, females 41). 94 nephropathic cystinosis patients were treated with either oral solution of cysteamine hydrochloride (N = 91) or phosphocysteamine (N = 3). The dose was approximately 54 mg/kg/day for cysteamine and phosphocysteamine. A historical control group was used from a randomised study of patients treated with ascorbic acid or placebo. The inclusion criteria were: proven nephropathic cystinosis with serum creatinine values less than 4 mg/dl (350 µmol/l), elevated leukocyte cystine content (> 0.2 nmol/hemicystine/mg protein) and no other known disease. The same inclusion criteria applied to the historical control.

Renal function

The patients treated with cysteamine showed a maintained mean creatinine clearance with values at entry and after 5 years of treatment of 43 and 47.4 ml/min/1.73m^2 respectively. Statistical comparison of creatinine clearance values between groups showed a significant difference in favor of the cysteamine group (p = 0.0006).

The number of cysteamine treated patients with a serum creatinine level below 10 mg/ml at age 6 was higher than that of controls (17 of 27 versus 2 of 17, respectively: odds ratio 12.8). Patients who started therapy with some degree of renal damage were less likely to respond.

No patients treated with cysteamine died but 12 out of 97 patients had renal death whereas 1 out of 17 patients in the historical placebo control died and 2 had renal death.

Growth

Standardised height was 86% of the 50th percentile at entry and 84% after 5 years of treatment indicating maintenance of growth rate in cysteamine treated patients.

Study 9148-2 was a retrospective and non-comparative study. Fifty-nine children with cystinosis (44 without transplant, 15 with renal transplant; 29 male patients and 30 male patients) were treated with cysteamine hydrochloride or phosphocysteamine in the United Kingdom. Only the non-transplanted patients were included in the efficacy analysis. The doses of cysteamine hydrochloride and phosphocysteamine were 34.4 and 36.5 mg/kg/day respectively. 26 patients received cysteamine hydrochloride and 18 patients phosphocysteamine.

Renal function

Cysteamine at relatively low doses slowed or prevented deterioration of glomerular function, based on creatinine clearance, which showed only a slight deterioration from baseline to 6 years (only 11 patients received treatment for 6 years).

Growth

This study demonstrated that cysteamine or phosphocysteamine therapy resulted in maintenance of growth rate in treated patients.

Survival

Of the evaluable patients, 3 (7%) required transplantation but started therapy late in the disease at 4.6 and 8 years of age. One of these patients died of multisystemic failure compatible with cystinosis.

There was no significant difference between pre-treatment and final values of white blood cells cystine concentrations. This is likely due to the lower dose used in this study with respect to study 9148-1. The general trend however was that patients who started treatment at an early stage with a reduction in white blood cells cystine can reach 10 years of age with an acceptable renal function.

Study 9148-3 was an open, multicentre study which included 93 naive patients (39 males and 38 females, with serum creatinine < 3 mg/ml and confirmed high levels of white blood cells cystine concentrations) and 46 patients who completed study 9148-1 (with serum creatinine < 4 mg/ml values without dialysis or transplant). The complete data of study 9148-3 up to the end of the trial in 1994 were provided.

Cysteamine hydrochloride or phosphocysteamine were randomly allocated and administered in solution every 6 hours at a dose of either 1.3 g/m^2/day or 1.95 g/m^2/day (equivalent to approximately 60 or 90 mg/kg/day respectively). The dosage calculations were made according to body surface in this study because patients might gain weight but might not catch up height, and this could result in an excessive dosage calculated only on the weight basis. 28 patients received cysteamine hydrochloride and 65 patients phosphocysteamine.

Renal function

The results indicated that cysteamine maintained glomerular function when treatment was started early, based on creatinine clearance levels and lack of dialysis or transplant.

Survival

Eight out of 46 (17%) long-term patients experienced renal death. Four patients underwent transplantation or dialysis. Two naive patients from the new patients group died but their deaths were not considered to be related to cysteamine therapy.

Growth

Growth rate was maintained in both dosage groups with no change in rate from start of therapy to the data cut-off point.

This study showed no difference in response between the two doses of approximately 60 or 90 mg/kg/day, given orally in four divided doses.

Following administration to children and adults with elevated leukocyte cystine concentrations, cysteamine free base at doses of 1.3 or 1.95 g/m2/day given in four divided doses reduced leukocyte cystine. In naive patients the mean leukocyte cystine level was 3.73 nmol/hemicystine/mg protein at entry. Levels fell with treatment and remained close to 1 nmol/hemicystine/mg protein after 36 months of treatment. However the recommended dosage did not seem to achieve the intended white blood cell cystine levels in a number of patients according to the postmarketing data submitted.

In summary, clinical studies have demonstrated that cysteamine was effective in preventing degradation of renal function, improving survival and growth rate in patients with cystinosis. In order to maintain white blood cells cystine below 1 nmol/hemicystine/mg protein, the oral dosage given in 4 divided doses was determined to be 50-60 mg/kg (1.3 g/m^2/day) in children under age 12 and under 50 kg of weight and 2 g/day given orally in four divided doses in older children and adults. Leukocyte cystine level has not been formally validated as a surrogate end point but its reduction is very suggestive of efficacy given the accepted pathophysiology of cystinosis. Nevertheless the dosage has to be adapted individually to reduce white blood cells cystine levels.

Oral cysteamine was not shown to prevent eye deposition of cystine crystal and it is not known whether cysteamine may prevent brain deposition of cystine, thereby preventing dementia.

Safety

Safety data are scarce concerning cysteamine bitartrate but information coming from other formulations trials is acceptable.

The safety evaluation is based on 246 patients in whom clinical observations and laboratory studies performed periodically. Adverse events were collected retrospectively (except in study 9148-3) but the reports were not prepared in a standardised manner.

The two dose levels used in study 9148-3 showed no significant difference except for naive patients who received phosphocysteamine. 11 patients (32%) experienced vomiting at 1.3 g/m^2/day whereas 21 (71%) at 1.95 g/m^2/day.

In **study 9148-1**, cysteamine was well tolerated. Nausea and vomiting were the main side effects observed. In the cysteamine group, 3 patients withdrew, one had a serious event (hepatic veno-occlusive disease probably related to cystinosis). 25 patients reported 33 events, 3 of which were serious and possibly related to cysteamine (one hospitalisation for dehydration after vomiting, one episode of moderate increase of ALT, AST and LDH and one episode of hallucinations).

In **study 9148-2**, 9 patients withdrew due to adverse events mostly gastrointestinal (nausea, vomiting, anorexia, diarrhoea and fever) and 2 other patients withdrew due to adverse events and disease progression (one of these patients died of multisystemic failure consistent with cystinosis).

In **study 9148-3**, 2 patients died but their deaths were not considered related to cysteamine therapy. 14 patients (10%) withdrew mostly due to gastrointestinal adverse events. No sudden or unexpected adverse events were observed.

Since the marketing authorisation in the United States of America, three serious adverse events have been reported. One case of stomach pain and skin discoloration, one case of Fanconi syndrome (proteinuria and hypoalbuminaemia) and one case of elevated blood glucose.

The most frequent adverse events were nausea, vomiting and anorexia. Skin rashes were reported. Other undesirable effects included seizures and hallucinations.

The applicant is keeping a register of the treated patients including data on their general clinical outcome and possible adverse effects. Furthermore the applicant proposed a form that would be provided with each order of the medicinal product and a form which would collect information on

patients who discontinue treatment. The applicant has been requested to provide analysis of this information gathered with these forms on a regular basis.

Benefit/risk assessment

Risk

About 70% of patients suffered from adverse effects. Some of them such as gastroduodenal irritation coincided with those foreseen in preclinical studies.

There is a concern with regard to the long-term use of cysteamine. The potential for bone marrow depression and for neuroendocrinological side effects in humans and the lack of complete mutagenicity or carcinogenicity animal studies may become particularly relevant with a medicinal product prolonging significantly life expectancy. Though no mutagnic concern was noted in Ames test and Mouse micronucleus test performed later.

Furthermore the reproduction studies do not allow concluding on a teratogenicity potential which is also a concern as women with cystinosis reach childbearing age.

Benefit

The three clinical trials strongly suggested that cysteamine delayed renal deterioration (as estimated by means of creatinine levels) and renal death (need for dialysis or renal transplantation) when treatment is started at an early age with good renal function. Treated children can reach the age of ten with an acceptable renal function whereas renal death is expected before that age in the natural course of the disease. Efficacy on renal function is less clear if treatment is started when renal failure is already marked.

Considering that nephropathic cystinosis is a fatal and rare disease and that cysteamine is already considered a useful drug with no alternative treatment (although not available as a proprietary medicinal product in the European Union), the risk-benefit ratio of Cystagon has to be considered favourable.

More information on the possible long-term side effects will be provided through the analysis of information gathered from a register of treated patients.

First Annual Reassessment

Orphan Europe submitted a dossier to the EMEA, Rapporteur, Co-Rapporteur and CPMP members in June 1998. At the request of the Rapporteur, Orphan Europe has updated this dossier to complete the information initially provided.

Orphan Europe submitted data on the extent of use of Cystagon in the European Union, a clinical expert comment on the new information provided since the marketing authorisation and a company comment indicating their experience and suggestions regarding the use of the patient follow-up forms.

The total number of patient treated in European Union during the period covered by this report as estimated from customer supply records seems to be around 280. As the company's expert pointed out, clinical experience remains limited because the patient population is very small. The CPMP requested the set up of a patient database based on the voluntary return of pre-defined treatment forms completed by the treating physician. At the end of June 1998, a total of 133 forms were collected. They relate to a total of 95 patients. Nothing unexpected has been identified in terms of efficacy or safety, but some relevant trends can be identified in terms of type of treatment:

- The total daily dose varied from 11 to 80 mg/kg/d (mean 42±14 mg/kg/d). While the recommended dose is 50 mg/kg/d in 4 doses per day for children under 12 years and 2g/d in 4 doses per day for children older than 12 years.
- The number of doses per day was 4 (or more) in only 60% of the patients.

In view of the lack of adherence to the recommended dose, it is not surprising that putative markers of efficacy, such as white blood cells cystine levels, the marker recommended in the SPC, do not reach the target values. (These are available only for 46 patients.)

The CPMP still thinks that keeping a systematic database of the treated patients is useful and will provide relevant data that could not be obtained otherwise in a drug/disease of this type. The data

already obtained on lack of adherence to the recommended therapy prove it. The small change in the follow-up forms themselves proposed by the company (to state the kidney transplantation status of the patient) is useful and acceptable. The CPMP welcomed the company's suggestion to send prescribers a letter in order to explain the usefulness of the patient follow-up forms, which should improve compliance. The company should also comment in the next PSUR the inter-laboratory variations in the method of measurement of cystine white cells levels.

Two periodic safety update reports have been provided covering the period from 1 September 1996 to 30 June 1998. In general, the reported adverse reactions were already included in the SPC and no further action in this respect was deemed necessary apart from slightly changing the wording of the overdose section, following the report of a progressive lethargy related to the overdose of cysteamine. The company's expert draws the attention to a recently published paper on the effects of cysteamine (HCI or plosphocysteamine, not Cystagon which is cysteamine bitartrate) on gastric acid output and serum gastrin levels. Cysteamine increased acid output and serum gastrin levels, and inflammation was observed in two subjects (duodenal mucosa in one case, gastric mucosa in the other). The expert suggests that the increased gastric acid output could be buffered by food and recommends that cysteamine should always be administered with food. In the current summary of product characteristics, there is no general recommendation in relation to food is given apart in children of 6 years of age or under. The company should discuss the convenience to recommend giving Cystagon with food.

The CPMP recommend that the marketing authorisation remains under exceptional circumstances. The CPMP agreed however to revise the list of specific obligations and follow-up measures to be fulfilled by the marketing authorisation holder.

Second Annual Reassessment

Pharmacokinetic data:

The submission of the expected pharmacokinetic study has been delayed due to various aspects including a slower recruitment of patients than expected. Nevertheless, the results should be submitted by end 1999.Results of a comparative bioavailability study evaluating three cysteamine derivatives (hydrochloride, bitartrate and phosphocysteamine) have been published in 1999. No statistical difference was found between relative bioavailabilities, AUC (0, ∞), Cmax and Tmax with each of the three salts of cysteamine tested.

Clinical data:

The approval of Cystagon by the CPMP was conditioned to a post-approval follow-up program, based on the collection of periodical clinical record forms from the treating physicians. Due to the limited number of clinical forms collected during the first year, the MA Holder was requested to make an effort in collecting these clinical forms.

The number of clinical forms collected has increased at the end of 1998; clinical forms were collected from around 52% (versus only one-third of the treated patients previously) but the MA Holder should continue to encourage doctors to fill in the forms. The importance of collecting such data with every drug supply visit is recalled.

Following assessment of first annual re-assessment, the CPMP requested the Marketing Authorisation to discuss the convenience to recommend giving Cystagon with food. Two six-month Periodic Safety Update Report were assessed since the First Annual Reassessment. The majority of the reported adverse reactions was already included in the SPC and did not change the benefit-risk ratio of the medicinal product. A case of overdose with progressive lethargy was reported in the second PSUR (see First Annual Reassessment). A type II variation was therefore requested by the CPMP to accordingly update the section of the SPC. The Marketing Authorisation Holder fulfilled this request and applied in the same time to add that Cystagon is better tolerated if taken after or with food.

Based on this data, the CPMP recommends that the marketing authorisation remains under exceptional circumstances. The CPMP agreed however to revise the list of specific obligations and follow-up measures to be fulfilled by the marketing authorisation holder.

5. Conclusion

The pharmaceutical dossier has mostly been made with already published data concerning cysteamine either as hydrochloride or phosphocysteamine or cysteamine bitartrate. Information on the major parts of the objections raised was provided. However, the question on impurity profile is not yet completely answered. Definite conclusions regarding the quality of the active substance will only be possible after submission and assessment of the report on the impurity profile study by Gas Chromatography/Mass Spectrometry.

The preclinical dossier is insufficient referring mainly to old bibliographical data on cysteamine as hydrochloride which are not up to current standards. There are toxicity data in only one species over a limited period of time. Genotoxicity data are insufficient but an *in vitro* clastogenic effect was demonstrated. Reproduction studies do not allow concluding on teratogenicity potential. Toxicological studies to determine the mutagenicity and genotoxicity were provided as part of the specific obligations. The results have been considered satisfactory and a type II variation has been submitted in order to accordingly update the SPC.

The clinical dossier included data demonstrating efficacy of cysteamine as hydrochloride and as phosphocysteamine to prevent degradation of renal function, improving survival and growth rate in patients with cystinosis. More information on the possible long-term safety will be provided through the analysis of information gathered from a register of treated patients.

Despite the deficiencies in the documentation provided and considering the favourable benefit/risk ratio for this potentially effective drug intended for a fatal and very rare disease, a marketing authorisation should be granted for this medicinal product under exceptional circumstances.

The indication is the following:

Cystagon is indicated for the treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure.

Cystagon treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis.

Since the Marketing Authorisation, in the view of additional data provided, the CPMP considered that the benefit/risk profile of cysteamine remained favourable and that the Marketing Authorisation remains under exceptional circumstances.