Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ancotil 2.5g/250ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each infusion bottle contains 2.5 g in 250 ml (1 g in 100 ml) of flucytosine.

Excipients with known effect: Each bottle contains 792 mg (34 mmol) sodium equivalent to 316 mg (14 mmol) in 100 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless to slightly yellow sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ancotil is indicated for the treatment of systemic yeast and fungal infections due to sensitive organisms: such infections include cryptococcosis, candidiasis, chromomycosis and infections due to *Torulopsis glabrata* and *Hansenula*.

In order to prevent the development of secondary antibiotic resistance, especially in the treatment of cryptococcal meningitis and severe systemic candidiasis, it is recommended that Ancotil should be given in combination with amphotericin-B. Amphotericin-B may also be given in combination with Ancotil in severe or chronic infections due to other organisms. In cases of cryptococcal meningitis, where toxicity of amphotericin B, or a combination of flucytosine with amphotericin B is dose limiting, a combination of flucytosine with fluconazole is recommended.

4.2 Posology and method of administration

Adults

Ancotil for Infusion should be administered using a giving set. It may be administered directly into a vein, through a central venous catheter, or by intra-peritoneal infusion. The recommended daily dosage in adults is 200mg/kg bodyweight divided into four doses over the 24 hours. In patients harbouring extremely sensitive organisms a total daily dose of 100 to 150mg/kg bodyweight may be sufficient.

Adequate effects can, however, often be obtained with a lower dose.

It is suggested that the duration of the infusion should be of the order of 20 to 40 minutes provided this is balanced with the fluid requirements of the patient.

Paediatric population

Available data are not sufficient to support evidence-based dosing recommendations in paediatric patients, including term and preterm neonates.

Flucytosine should not be used as first line or monotherapy in paediatric patients. Flucytosine should be used in combination with other appropriate anti-fungal agents when other suitable drugs are not available and are not likely to be effective.

Duration of treatment

The duration of treatment should be determined on an individual basis. The outcome of therapy will be affected by variations in the sensitivity of the infecting organism, its accessibility and its susceptibility to Ancotil, as well by differences in the response of individual patients.

For example, in acute Candida sepsis treatment may be only a matter of weeks; sub-acute and chronic cases should usually be treated for many months. The following is a guide:

- systemic candidiasis 2 - 4 weeks
- cryptococcus meningitis 1 - 10 weeks
- chromomycosis 6 - 12 months

Use in patients with renal insufficiency

Since Ancotil is excreted primarily by the kidneys, doses should be administered with extended intervals in patients with renal impairment based on creatinine clearance and according to the following schedule:

In patients with:

Creatinine Clearance (ml/min)	Dose (mg/kg)	Dose interval (hours)
> 40	25 - 50	6
40 - 20	25 - 50	12
20 - 10	25 - 50	24
< 10	25 - 50	Determine flucytosine serum concentration 12 hours after first dose. Subsequent doses should be calculated according to the results of regular monitoring of the serum concentration of the drug, which should not be allowed to exceed 80 micrograms/ml. Blood levels of 25 to 50 micrograms/mL are normally effective.

Patients under haemodialysis

Flucytosine is filtered and excreted during the haemodialysis therefore the dosage of Ancotil must be repeated after the session of haemodialysis.

In anuric or nephrectomized haemodialysis patients, under no circumstances should the single dose be infused prior to performing the next dialysis session.

Liver impairment

Patients with impaired liver function may be treated with flucytosine, but they require particularly careful monitoring.

Antifungal combinations and Amphotericin B

The combination therapy of Ancotil plus amphotericin B has a synergistic effect and therefore it is sometimes possible to reduce the dosage and thus diminish the risk of secondary resistance to flucytosine. This combination is indicated in certain sub-acute and chronic fungal infections, especially with meningo-encephalitides, endocarditides and aspergilloses. The recommended dose of flucytosine for this combination therapy is 100-150 mg/kg Ancotil daily. Particularly careful monitoring of renal function is necessary when flucytosine is combined with amphotericin B. The Summary of Product Characteristics of amphotericin B and international accepted guidelines of infectious diseases should be considered.

Elderly

Although no specific studies have been performed to establish the use of Ancotil in the elderly, documented use has indicated that the dosage requirements and side effect profile are similar to those of younger patients. Particular attention should be paid to renal function in this group.

Ancotil for Infusion may be given concurrently with other infusions of normal saline, glucose or glucose/saline. No other agent should be added to or mixed with Ancotil for Infusion.

4.3 Contraindications

Ancotil is contra-indicated:

- in patients who have shown hypersensitivity to flucytosine or any of the excipients.
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)
- in co-administration of Ancotil with irreversible inhibitors of the dihydropyrimidine dehydrogenase enzyme (DPD) e.g. brivudine, sorivudine and their analogues (see section 4.4 and 4.5).
- in breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Paediatric population
Flucytosine has a narrow therapeutic window and there is a risk of its potential toxicity at high systemic concentrations.

Because of prolonged elimination of flucytosine in paediatric patients, especially in term and preterm neonates, flucytosine administration may lead to exceeding the optimum serum levels. Monitoring of plasma flucytosine levels based on local (or national) antifungal treatment guidelines and dose adjustments, as needed, are necessary to avoid excessive exposure to flucytosine.

The blood count and kidney function should be regularly controlled in paediatric patients during the treatment to monitor creatinine concentration and clearance.

Sensitivity testing:

It is recommended that cultures to identify the strain for sensitivity testing be taken before treatment and repeated at regular intervals during therapy. However, it is not necessary to delay treatment until results of these tests are known.

For sensitivity testing it is essential that culture media are free of antagonists to flucytosine.

Haematological status and liver function
The haematological status and the liver function (SGOT, SGPT and alkaline phosphatase) should be determined before commencement of treatment and further regular monitoring is advised, especially at the beginning of the treatment (recommended daily during the first week of treatment and twice weekly thereafter).

Patients with impaired liver function may be treated with flucytosine; however, they require particularly careful monitoring.

The product should be used with great caution in patients with depression of bone marrow function or blood dyscrasias. In patients undergoing cytostatic or immunosuppressive therapy blood counts must be monitored more frequently because of high risk of haematological damage.

Renal function and haemodialysis
The excretion of flucytosine drug takes place exclusively at kidney level. Therefore, before and during treatment with Ancotil renal function of the patient should be determined (preferably by determining the endogenous creatinine clearance). If necessary, the dose should be adjusted (see section 4.2).

Creatinine Measurement: Flucytosine may interfere with the two-stage enzymatic determination of creatinine resulting in a false positive azotemia. Other methods for the determination of creatinine should be used. Flucytosine has no impact on a Jaffe's reaction test.

Ancotil should not be used in patients with impaired renal function in the absence of facilities for monitoring blood levels of the drug.

65 to 75% of Ancotil is excreted by haemodialysis. Consequently, for patients undergoing haemodialysis, the dose of Ancotil must be administered again after each haemodialysis or purification session.

Flucytosine serum levels
Steady-state serum level should average 25 to 50 µg/ml. Lower levels may be sufficient for more sensitive strains. In vitro sensitivity of most of the susceptible strains lies at minimum inhibitory doses between 10 and 25 µg/ml. However, the dosage should ensure that serum levels greater than 25 µg/ml are maintained due to the increased risk of development of resistance at low concentrations. Prolonged existence of serum levels above 100 µg/ml should be avoided because of increased haematological toxicity at high levels.

Moreover, the 5-FC levels should be monitored in order to adjust the dosage accordingly. When measuring drug serum levels it should be noted that levels of the drug in blood samples, taken during or immediately after administration of Ancotil infusion, are not a reliable guide to subsequent levels; it is advisable to remove blood for monitoring of blood levels of Ancotil shortly before starting the next infusion.

Dihydropyrimidine dehydrogenase enzyme (DPD) deficiency
5-Fluorouracil is a metabolite of flucytosine. DPD is a key enzyme involved in the metabolism and elimination of 5-fluorouracil. Therefore, the risk of severe drug toxicity is increased when Ancotil is used in individuals with deficiency in dihydropyrimidine dehydrogenase (DPD). Determination of DPD activity may be considered where drug toxicity is confirmed or suspected. In the event of suspected drug toxicity, consideration should be given to stopping Ancotil treatment.

Nucleoside analogues such as brivudine and sorivudine are potent inhibitors of the DPD enzyme and may therefore cause an abrupt rise in the plasma concentration of 5-fluorouracil and/or other fluoropyrimidines. An interval of at least 4 weeks must elapse between treatment with brivudine, sorivudine and their analogues and initiation of a therapy with Ancotil.

Patients receiving co-administered phenytoin and Ancotil should be regularly monitored for increased plasma concentrations of phenytoin (refer to section 4.5 for further details)

The combination therapy of Ancotil plus amphotericin B has a synergistic effect. However, it should be remembered that this combination increases the risk of side-effects.

Contraception in males and females
Flucytosine is partially metabolised into 5-fluorouracil, which is genotoxic and considered as a potential human teratogen.

Females of childbearing potential under treatment must use effective contraceptive during treatment and for 6 months after treatment. In case of renal impairment, the contraception period should be prolonged for additional two months.

Male patients (or their female partners of childbearing potential) must use effective contraception during treatment and for three months after treatment. In case of renal impairment, the contraception period should be prolonged for additional two months.

Excipients
This medicine contains 792 mg sodium per bottle (250 ml), equivalent to 40 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ancotil is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interactions

There is contradictory evidence concerning a drug interaction between flucytosine and cytarabine (cytostatic cytosine). The antimycotic effects of flucytosine might be impaired by cytarabine. Strict monitoring of blood levels is required if the two medicines are given concurrently.

Brivudine, sorivudine and analogues are potent inhibitors of DPD, a fluorouracil metabolising enzyme (see section 4.4). As fluorouracil is a metabolite of flucytosine, concomitant administration of these drugs with Ancotil is contraindicated (see section 4.3).

Caution should be applied when myelosuppressive agents are co-administered, because of a potential risk of increased toxicity.

Increased phenytoin plasma levels have been reported with concomitant administration of phenytoin and intravenous fluorouracil, leading to symptoms of phenytoin intoxication (see section 4.4). This is relevant to Ancotil as flucytosine is metabolised to fluorouracil. Although administration of Ancotil results in much lower plasma concentrations of fluorouracil, this interaction cannot be entirely excluded. Therefore, patients receiving co-administrated phenytoin an Ancotil should be regularly monitored for increased plasma concentrations of phenytoin.

Concomitant administration of flucytosine and nephrotoxic substances require extremely careful monitoring of renal function. Medicines which affect glomerular filtration prolong the half-life of flucytosine.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Flucytosine is partially metabolised into 5-fluorouracil, which is genotoxic and considered as a potential human teratogen (see section 5.3).

Females of childbearing potential under treatment must use effective contraceptive during treatment and for 6 months after treatment. In case of renal impairment, the contraception period should be prolonged for additional two months.

Male patients (or their female partners of childbearing potential) must use effective contraception during treatment and for three months after treatment. In case of renal impairment, the contraception period should be prolonged for additional two months.

Pregnancy
In animal studies flucytosine and one of its metabolites (5-fluorouracil) showed reproductive toxicity (teratogenicity and embryotoxicity) (see section 5.3).

In humans flucytosine crosses the placenta. There are very limited data on use of flucytosine in pregnant women. Therefore, harmful impact on the embryo/foetus cannot be excluded, especially during the first trimester. Consequently, Ancotil should not be used during pregnancy and in women of childbearing potential not using contraception unless strictly necessary in case of life-threatening infections and lack of an effective alternative treatment.
If Ancotil is administered in pregnancy, the patient should be advised of the teratogenic risk of Ancotil, and careful prenatal and postnatal monitoring should be performed. In case of administration up to delivery, in view of the safety profile of flucytosine, a neonatal monitoring (hematologic and hepatic) should be performed.

Breastfeeding
There are no data on the excretion of flucytosine in human milk. Breastfeeding is contraindicated during flucytosine treatment. (see section 4.3).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Undesirable effects of flucytosine primarily affect the gastrointestinal tract, liver and bone marrow. Serious side effects may occur with elevated serum concentrations of flucytosine (e.g. in renal insufficiency, if the dose is not adjusted to the reduced renal excretion capacity).

Assessment of undesirable effects is based on the following frequency categories:

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)
Not known (Frequency cannot be estimated from the available data)

The following undesirable effects have been observed:

Organ systems	Common	Uncommon	Rare
Blood and lymphatic system disorders	Haematological changes, such as anaemia, leukopenia, neutropenia, granulocytopenia and thrombocytopenia, dependent on possibly elevated serum levels		Agranulocytosis, eosinophilia, aplastic and haemolytic anaemia, bone marrow toxicity (irreversible) associated with pancytopenia and bone marrow suppression in immunosuppressed patients with fatal outcome
Immune system disorders			Hypersensitivity (e.g. Lyell's syndrome, skin rash, pruritus, urticaria)
Metabolism and nutrition disorders			Hypokalaemia
Psychiatric disorders		Confusion,	Hallucinations,
Nervous system disorders		Headache, sedation	Convulsions, paraesthesia, peripheral neuropathy
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			Cardiotoxicity, ventricular dysfunction, arrhythmias
Respiratory, thoracic and mediastinal disorders		Dyspnoea, chest pain, respiratory arrest	Acute respiratory insufficiency
Gastrointestinal disorders	Gastrointestinal discomfort (diarrhoea, nausea, vomiting)	Abdominal pain	Ulcerative colitis
Hepatobiliary disorders	Impaired liver function, reversible elevation of serum transaminases		Hepatitis, liver cell necrosis with fatal outcome
Skin and Subcutaneous tissue disorders		Skin rash,	
Renal and urinary disorders			Renal insufficiency

In the majority of the cases, these disorders occur within the first 2 to 3 weeks of treatment.

Undesirable effects may occur more frequently with combination therapy with amphotericin B and other potentially nephrotoxic compounds. Thus, flucytosine serum levels may be increased if the dose is not adjusted in accordance with the reduced renal function.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Signs and symptoms

Likely symptoms of overdose include nausea, vomiting, diarrhoea and abdominal pain, blood count changes, especially leukopenia and thrombocytopenia, and elevated liver enzyme levels in serum.

Management
There is no specific antidote. Milder toxic effects such as nausea, vomiting, diarrhoea, bone marrow damage and elevated liver transaminases are usually completely reversible after discontinuation of treatment.

After ingestion, further absorption may be prevented by inducing vomiting or gastric lavage and then administration of activated charcoal and sodium sulphate as a laxative.

Forced diuresis is indicated as soon as possible.

Haemodialysis may be considered and will produce a rapid fall in the serum concentration of Ancotil.

Further treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic agent

ATC Code: J02AX01

Flucytosine is a fluorinated pyrimidine derivative. It is an antimycotic agent exerting fungistatic and fungicidal activity by interfering with protein and DNA synthesis. In contrast to mammalian cells, fungi cells absorb flucytosine selectively via cytosine permease. It is deaminated to 5-fluorouracil which is then incorporated into cell RNA where it induces faulty protein biosynthesis. In addition, DNA synthesis is inhibited by 5-fluorouracil blocking thymidylate synthesis. Flucytosine has fungistatic and fungicidal activity in systemic and local infections against yeasts such as Candida, Torulopsis and Cryptococcosis as well as in chromomycosis. In aspergilli, it shows exclusively fungistatic activity.

Antimycotic activity
An in vitro study on susceptibility of approximately 8,800 clinical isolates (yeasts and filamentous fungi) to flucytosine according to NCCLS (The National Committee for Clinical Laboratory Standards) guidelines demonstrated that the four most common Candida species are extremely sensitive (the minimal inhibitory concentration for Candida species varied from 0.12 µg/ml to 1 µg/ml for 90% of the tested strains).
Primary resistance has been observed in some fungi. However, it occurs only very rarely with Candida spp. (95% susceptible, 2% intermediary, 3% resistant), except for C. krusei (5% susceptible, 67% intermediary, 28% resistant).
Secondary resistance may develop, in particular with flucytosine monotherapy. Strains initially susceptible to Ancotil may become resistant during therapy. It is thus recommended to estimate the susceptibility of the strains before and during therapy. Combination of flucytosine and other antimycotic agents such as amphotericin B and triazoles often result in a synergistic effect; the MIC value achieved with the combination is less than the MIC values of the individual substances.

5.2 Pharmacokinetic properties

Absorption: orally administered, at least 90% is rapidly absorbed. The concentration achieved is the same as that obtained after the same dose is given by short intravenous perfusion.

Distribution: Ancotil is widely distributed in body tissues and fluids (including cerebrospinal fluid). The volume of distribution is between 0.5 and 1.0 l/kg. Binding to plasma proteins is minimal (< 5%) and therefore it can be easily removed by haemodialysis. Virtually the total amount of a single dose is removed by haemodialysis. Consequently, a full dose must be administered again after each haemodialysis session.
The urinary concentrations of Ancotil may be up to 100 times higher than plasma concentrations, in patients with a normal renal function.

Metabolism: Only very small amounts of flucytosine are metabolised. Bacteria in the bowels are probably responsible for some metabolism of flucytosine to 5-fluorouracil (5-FU). The 5- FU/5-FC ratio of plasma concentrations is low (4%).

Excretion: The plasma half-life is 3-6 hours in patients with normal renal function but this value increases in renal failure (30-250 hours). Excretion is almost exclusively through glomerular filtration. About 90 % of the dose administered is excreted unchanged in the urine.

Paediatric population

The limited data available on flucytosine pharmacokinetic properties in paediatric patients suggest that in children, especially neonates flucytosine half-life is longer than in adults (4 vs 7 h). One neonatal pharmacokinetic study demonstrated that flucytosine half-life was twice as that reported in adults, although peak concentrations were comparable. Additionally, the volume of distribution of flucytosine approximates the volume of total body water due to its high solubility. In a retrospective study of 391 paediatric patients, 65 % of flucytosine trough concentrations exceeded the normal reference range.

5.3 Preclinical safety data

In vitro investigations on mutagenic potential of flucytosine were negative. No studies are available on the carcinogenic potential of Ancotil.
Flucytosine has been shown to be teratogenic and embryotoxic in rats when given in oral or parenteral doses of 40 mg/kg body weight per day onwards (240 mg/m2 or 0.043 times the human daily dose).

The flucytosine metabolite 5-fluorouracil is genotoxic in mice and in vitro, embryotoxic and teratogenic in mice and rats, and is classified as possible human teratogen. Malformations occurred (defects in the nervous system, palate, skeleton, tails, limbs) in several species (including rat and Syrian golden hamsters). Embryotoxic effects (small foetus, resorption) are also observed in monkeys treated with 5-fluorouracile.
Both flucytosine and 5-fluorouracil cross the placenta.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Tromethamine
Hydrochloric acid 25% (for pH adjustment)
Water for injection

6.2 Incompatibilities

Ancotil for Infusion may be given concurrently with other infusions of Sodium Chloride intravenous infusion (0.9% w/v) BP, Glucose intravenous infusion (5% w/v) BP, or Sodium Chloride (0.18%) and Glucose (4% w/v) intravenous infusion BP. No other agent should be added to or mixed with Ancotil for Infusion.

6.3 Shelf life

Unopened: 2 years.

Once opened: From a microbiological point of view, once opened the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours when stored between 18 and 25°C. Unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Ancotil for Infusion should be stored between 18^{o}C and 25^{o}C.

If stored below 18^{o}C, precipitation of Ancotil substance may occur.

Prolonged storage above 25°C could lead to the decomposition of Ancotil resulting in the formation of 5-fluorouracil.

6.5 Nature and contents of container

Colourless Type II, neutral glass bottle containing 250 ml. The bottles are closed with Teflon coated butyl rubber stoppers and aluminium crimp. Bottles are in packs of 5.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Ancotil for Infusion is available to hospitals only.

Ancotil should be visually inspected for particulate matter, preciptation and discolouration prior to administration. Only clear and colourless or almost colourless solution should be used.

For single use only. Discard any remaining contents after use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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