Package leaflet: Information for the patient

Ancotil® 2.5 g/250 ml (1g in 100 ml) Solution for Infusion
Flucytosine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- This leaflet tells you about Ancotil. It does not contain all the information about Ancotil.
- If you have any further questions, or are unsure of anything, ask your doctor or nurse.
- If you get any side effect, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHATS ANCOTIL IS AND WHAT IT IS USED FOR
Ancotil Solution for Infusion contains the active substance flucytosine, which is an anti-fungal agent. It is used to treat certain yeast and fungal infections.

2. BEFORE YOU ARE GIVEN ANCOTIL SOLUTION FOR INFUSION
You should not be given Ancotil:
- If you are allergic (hypersensitive) to flucytosine or any of the other ingredients of Ancotil (these are listed in section 6, “Further Information”).
- If you are using any medicine known as an irreversible inhibitor of the dihydropyrimidine dehydrogenase enzyme [DPD], (e.g. brivudine, sorivudine). These medicines are usually used to treat chickenpox and shingles.
- If you are taking a combination medicine containing tegafur/gimeracil/oteracil, used in the treatment of cancer of the stomach, large intestines or rectum
- If you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency).
- If you are breast-feeding.

Warnings and precautions
Tell your doctor before you start treatment if you have a liver, kidney or blood problem. Your doctor may need to carry out blood tests during your treatment.
Regular blood and kidney monitoring may also need to be carried out if children are treated with Ancotil, (see section 3 – ‘How Ancotil is Given’).

Females of childbearing potential under treatment must use effective contraceptive during treatment and for 6 months after treatment. Male patients (or their female partners of childbearing potential) must use effective contraception during treatment and for three months after treatment. In case of reduced kidney function, the contraception period should be prolonged for additional two months. (See Pregnancy and breastfeeding section).

Other medicines and Ancotil

Tell your doctor before you start treatment if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor if you are taking;

- cytarabine (which is used to treat certain leukaemias)
- medicines to treat chickenpox or shingles (e.g. brivudine and sorivudine) or have used them in the last 4 weeks
- medicines that stop or slow the formation of blood cells in the bone marrow (myelosuppressants)
- medicines for epilepsy containing phenytoin, your doctor may do some blood tests
- medicines which can affect your kidney function

Also tell your doctor if you are having, or have recently had, treatment with tegafur/gimeracil/oteracil.

Pregnancy, breast-feeding and fertility

You must tell your doctor before you start treatment if you are pregnant, if you think you may get pregnant or if you are breast-feeding.

- Your doctor will decide whether you should be given Ancotil if you are pregnant. If Ancotil is administered in pregnancy, there is a risk of causing malformations (abnormally formed parts of the body) to the unborn baby and careful before and after birth monitoring should be performed.
- You should not be given Ancotil if you are breast-feeding.

Contraception in males and females

Females of childbearing potential under treatment must use effective contraceptive during treatment and for 6 months after treatment. Male patients (or their female partners of childbearing potential) must use effective contraception during treatment and for three months after treatment. In case of reduced kidney function, the contraception period should be prolonged for additional two months.

Ancotil contains Sodium Chloride

This medicine contains 0.8 g sodium (main component of cooking/table salt) in each unit volume. This is equivalent to 40% of the recommended maximum daily dietary intake of sodium for an adult.

3. HOW ANCOTIL IS GIVEN

Ancotil is administered only in a hospital and is administered by a doctor or nurse. It is usually given into a vein or by a procedure called “intraperitoneal infusion” while you are in hospital, usually over a 20-40 minute period. Ancotil can be given with a glucose and/or saline infusion. It should not be mixed in the same solution with other medicines.

Ancotil may be used alone, or when treating certain fungal infections, in combination with other medicines.

Your doctor will determine the most appropriate dose for you to be given. The usual total daily dose is 100 to 150 mg/kg bodyweight in divided doses. In some instances, you may be given up to a total daily dose of 200 mg/kg bodyweight in divided doses.

Smaller doses may be given at extended intervals to patients with kidney problems.

Patients with liver problems need careful monitoring whilst being treated with Ancotil.

The treatment period with Ancotil will be determined by your doctor and will vary on a patient by patient basis.

Use in Children

There is not enough clinical data available for dosing recommendations in children. If this medicine is prescribed to your child, the doctor will choose the most appropriate dose.

Throughout treatment, your child's blood will be regularly tested to ensure flucytosine levels do not go over the optimum blood levels.

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor straight away if you notice any of the following side effects:
- allergic reaction, the signs of which may include swelling of your face, lips and throat, difficulty breathing with wheezing, severe blistering and peeling of skin, skin rash, itching, or raised red blotchy skin
- inflammation of the liver, (hepatitis) or liver cell death, the symptoms of which can include muscle and joint pain, fever, dark urine, pale faeces, and yellowing of the eyes and skin (jaundice)
- reduced kidney function, indicated by changes to your urine output
- changes in your blood cell levels detected by blood tests

Other side effects include;
Common: may affect up to 1 in 10 people
- diarrhoea, nausea, vomiting

Uncommon: may affect up to 1 in 100 people
- confusion, sensing things that are not really there (hallucinations)
- fits, headache, sedation
- feeling of dizziness or 'spinning' (vertigo)
- heart muscle damage

Rare: may affect up to 1 in 1,000 people
- reduced liver function, reversible raised levels of liver enzymes

Not known: frequency cannot be estimated from the available data
- low levels of potassium in the blood
- tingling or prickling feeling 'pins and needles', pain, numbness or weakness in your hands, arms or feet
- irregular heartbeat
- chest pain
- abdominal pain, inflammation and ulcers in your digestive tract (ulcerative colitis)

If you are concerned about any of these side effects, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

For the United Kingdom:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

5. HOW ANCOTIL SOLUTION FOR INFUSION IS STORED
- All medicines should be kept out of the sight and reach of children.
- Hospital staff should store Ancotil between 18 °C and 25 °C.
- This product should not be used after the expiry date shown on the bottle label after "EXP". The expiry date refers to the last day of that month.
- Before administration, Ancotil should be visually inspected for any particulate matter and discolouration.
- Do not use Ancotil if you notice that there are any visible particles, precipitation or discolouration.

- For single use only. Discard any remaining contents after use.
- The product should only be handled by experienced healthcare professionals.
- Medicines should not be disposed of via wastewater or household waste. The pharmacist should provide instructions as to how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ancotil Solution for Infusion contains

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

Other ingredients: Sodium chloride, tromethamine, hydrochloric acid, and water for injections.

What Ancotil Solution for Infusion looks like and contents of the pack

- Ancotil Solution for Infusion is a clear, colourless to slightly yellow solution.
- Ancotil Solution for Infusion is available in packs of 5 bottles of 250 ml.

Marketing Authorisation Holder and Manufacturer

Viatris Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

Manufacturer

Meda Pharma GmbH & Co. KG,
Benzstrasse 1, 61352 Bad Homburg, Germany.

For any information about this medicine, please contact the Marketing Authorisation Holder

This leaflet was last revised in October 2025.

Package leaflet: Information for the user

Ancotil® 2.5 g/250ml (1g in 100 ml) Solution for Infusion
Flucytosine

This leaflet provides technical information about Ancotil for the healthcare professional.
The tear-off portion attached is intended for the patient.

Uses
Therapeutic properties and Indications
Ancotil is a fluorinated pyrimidine effective in the treatment of certain systemic fungal infections. In fungi sensitive to the preparation, it acts as a competitive inhibitor of uracil metabolism.
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 *Candida glabrata* and *Hansenula*.

Pharmacokinetics
Bioavailability after a 2 g oral dose varies between individuals and ranges from 76-98%. Peak plasma concentrations are reached within 1-2 hours after oral administration but may be delayed in subjects with renal impairment to 4-6 hours. Food and antacids decrease the absorption rate, but the total extent absorbed is not relevantly affected. Ancotil is widely distributed in body tissues and fluids (including cerebrospinal fluid). The volume of distribution is 0.5-1.0 l/kg. Binding to plasma proteins is minimal (<5%). Typical maximum serum concentrations are 30-50 ug/ml after oral intake or IV administration of 2 g flucytosine. Concentrations in cerebrospinal fluid, saliva and peritoneal fluid are slightly lower. Flucytosine crosses the human placenta and accumulation in amniotic fluid has been observed. Urinary concentrations may be up to 100 times higher than plasma concentrations (normal renal function). Only a small proportion of flucytosine is metabolised. Enteric bacteria may be responsible for some metabolism of flucytosine to 5-FU. Additionally, 5-FU is released from killed fungi cells. The 5-FU/5-FC ratio of plasma concentrations is low (4%). 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. Flucytosine is readily removed by haemodialysis, consequently, a full dose must be administered again after each haemodialysis session. Elimination via peritoneal dialysis is possible.

Dosage and 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 intraperitoneal infusion. The recommended daily dosage in adults is 200 mg/kg bodyweight divided into four doses over the 24 hours. In patients harbouring extremely sensitive organisms, a total daily dose of 100 to 150 mg/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. As a rule, treatment with Ancotil for Infusion should rarely be required for periods of more than one week.
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% w/v) and glucose (4% w/v), intravenous BP, however other agents should not be added to or mixed with Ancotil for Infusion.

Renal impairment
Since Ancotil is excreted primarily by the kidneys, patients with renal impairment should be given smaller doses at extended intervals, based on creatinine clearance. The following is suggested as a guide for dosage in patients with severe infection associated with renal impairment:

In patients with:
creatinine clearance > 40 ml /min: 25-50 mg/kg every 6 hours.
creatinine clearance <40 to >20 ml/min: 25-50 mg/kg every 12 hours.
creatinine clearance <20 to >10 ml/min: 25-50 mg/kg every 24 hours.
creatinine clearance <10 ml/min: an initial single dose of 25-50 mg/kg;
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 haemodialysis, therefore the dosage of Ancotil must be repeated after the session of haemodialysis.
In anuric or nephrectomized haemodialysis patients, the initial single dose should not be repeated before performing the next dialysis session.

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

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

Paediatric population
Available clinical data are not sufficient to support exact dosing recommendations in children. 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.
If this medicine is prescribed, the doctor will choose the most appropriate dose.
Because of prolonged elimination of flucytosine in paediatric patients, especially in very young children, flucytosine administration may lead to exceeding the optimum blood levels. Therefore, throughout the treatment the child's blood will be regularly tested for flucytosine levels.

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 as by differences in the response of individual patients. In cases of cryptococcal meningitis, treatment should last for at least 4 months.

Antifungal combinations and Amphotericin B
In the treatment of cryptococcal meningitis and severe systemic candidiasis it is recommended that Ancotil should be given in combination with amphotericin-B. This combination may also be given in certain sub-acute and 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 has demonstrated successful cure, but at a lower rate than in combination with amphotericin B.
The combination therapy of Ancotil plus amphotericin B has a synergistic effect and therefore it is possible to reduce the dosage and thus diminish the risk of secondary resistance to flucytosine. The recommended dose of flucytosine for this combination therapy is 100-150 mg/kg Ancotil daily. Particularly careful monitoring of renal function is necessary. The Summary of Product Characteristics of amphotericin B and international accepted guidelines of infectious diseases should be considered.

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.

Contra-indications and warnings

Contra-indications

Ancotil is contra-indicated in patients who

- have shown hypersensitivity to flucytosine or any of the excipients
- have known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- are being treated with tegafur/gimeracil/oteracil or antiviral nucleoside drugs (e.g. brivudine, sorivudine and their analogues), see Drug interactions section
- are breast-feeding (see Fertility, pregnancy and lactation section)

Precautions

The haematological status, the renal function (preferably by determining the endogenous creatinine clearance) and the liver function (SGOT, SGPT and alkaline phosphatase) should be determined before starting treatment and regularly thereafter, especially at the beginning of the treatment. This should occur at least weekly in patients with renal insufficiency or blood dyscrasias. If necessary, the dose should be adjusted accordingly.

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.
Ancotil should not be used in patients with impaired renal function in the absence of facilities for monitoring blood levels of the drug.
Patients with impaired liver function may be treated with flucytosine; however, they require particularly careful monitoring.

Creatinine measurement

Flucytosine may interfere with the two-stage enzymatic measurement of creatinine used with the manual, desk-top Vitros DT 60 analyser, giving the false impression of azotemia. Other suitable methods should be used for creatinine assessment. The current creatinine method used with automated Vitros analysers is not affected by flucytosine. Flucytosine has no impact on a Jaffe's reaction test.

Flucytosine serum levels

Steady-state serum level should average 35 to 70 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-Fluorouracil metabolite levels should also 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 for 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. In calculating the fluid and electrolyte intake of patients with impaired renal function, cardiac failure or electrolyte imbalance, due allowance should be made for the volume and sodium content (138 millimole/litre) of Ancotil for Infusion.

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. Consideration should also be given to stopping Ancotil treatment.

Sensitivity testing
It is recommended that cultures 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.
To determine sensitivities, the methods of Shadomy (Appl Microbiol, 1969, 17, 871) and Scholer (Mykosen, 1970, 13, 179) are recommended.
For sensitivity testing it is essential that culture media are free of antagonists to flucytosine.

Sodium
Ancotil contains 34.5 mmol (or 0.8g) sodium/250ml solution for infusion. To be taken into consideration by patients on a controlled sodium diet.

Drug interactions
There is contradictory evidence concerning a drug interaction between flucytosine and cytarabine. The antimycotic effect of flucytosine might be impaired by cytarabine. Strict monitoring of blood levels is required if the two medicines are given concurrently.
An interval of at least 4 weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of Ancotil, concomitant use is contraindicated. An interval of at least 7 days should be observed when taking tegafur/gimeracil/oteracil and subsequent use of flucytosine.
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. Patients receiving phenytoin and Ancotil concomitantly should be checked regularly for increased phenytoin plasma levels.
Concomitant administration of flucytosine and nephrotoxic substances require extremely careful monitoring of renal function, since medicines which affect glomerular filtration prolong the half-life of flucytosine.

Fertility, pregnancy and lactation
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/m^2 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-FU.
Females of childbearing potential under treatment must use effective contraceptive during treatment and for 6 months after treatment. Male patients (or their female partners of childbearing potential) must use effective contraception during treatment and for three months after treatment. In case of reduced kidney function, the contraception period should be prolonged for additional two months.

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 in flucytosine, a neonatal monitoring (haematologic and hepatic) should be performed.

There are no data on the excretion of flucytosine in human milk. Breastfeeding is contraindicated during flucytosine treatment.

Possible side 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).

Undesirable effects based on frequency categories:
Common (≥ 1/100 to < 1/10)
- Gastrointestinal discomfort (diarrhoea, nausea, vomiting)
- Skin rash

Uncommon (≥ 1/1 000 to < 1/100)
- Allergic reactions, Lyell's syndrome
- Confusion, hallucinations
- Convulsions, headache, sedation
- Vertigo
- Cardiotoxicity ventricular dysfunction

Rare (≥ 1/10 000 to < 1/1 000)
- Impaired liver function, reversible elevation of serum transaminases, hepatitis, liver cell necrosis with fatal outcome

Not known: frequency cannot be estimated from the available data
- Haematological changes, such as anaemia, leukopenia, neutropenia, granulocytopenia and thrombocytopenia, dependent on possibly elevated serum levels
- Agranulocytosis, eosinophilia, aplastic anaemia, bone marrow toxicity (irreversible) associated with pancytopenia and bone marrow suppression in immunosuppressed patients with fatal outcome
- Pruritus, urticaria
- Hypokalaemia
- Paraesthesia, peripheral neuropathy
- Arrhythmias
- Acute respiratory insufficiency, dyspnoea, chest pain, respiratory arrest
- Abdominal pain, ulcerative colitis
- Renal insufficiency

In the majority of the cases, these disorders occur within the first 2 to 3 weeks of treatment. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Treatment of overdosage
Symptoms of overdose may include nausea, vomiting, diarrhoea and abdominal pain, blood count changes, especially leukopenia and thrombocytopenia, and elevated liver enzyme levels in serum. There is no specific antidote. Milder toxic effects are usually completely reversible after discontinuation of treatment. Forced diuresis is indicated as soon as possible. Haemodialysis produces a rapid fall in the serum concentration of Ancotil.

Pharmaceutical particulars
Ancotil comes in infusion bottles containing 2.5 g flucytosine in 250 ml sodium chloride solution. Other excipients are sodium chloride, tromethamine, hydrochloric acid and water for injections. The solution is colourless to slightly yellow.

Before administration Ancotil should be visually inspected and should not be used in the presence of visible particulate matters, precipitation and discolouration.
For single use only. Discard any remaining contents after use.
Ancotil for Infusion should be stored between 18 °C and 25 °C.
If stored below 18 °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.
Ancotil for Infusion 2.5 g in 250 ml in packs of 5.
Ancotil for Infusion is available to hospitals only

Marketing Authorisation Holders:
Viatris Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

Manufacturer:
Meda Pharma GmbH & Co. KG, Benzstrasse 1, 61352 Bad Homburg, Germany.

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