Patient Information Leaflet

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

Flucytosine

Read all of this leaflet carefully before you start using this medicine.

- 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 questions or are unsure of anything ask the doctor or nurse.
- If you experience any side effect and this becomes serious, tell your doctor or pharmacist.

In this leaflet:

1. What Ancotil is and what it is used for
2. Before you are given Ancotil
3. How Ancotil is given
4. Possible side effects
5. How Ancotil is stored
6. Further information

1. WHAT ANCOTIL IS AND WHAT IT IS USED FOR

Ancotil Solution for Infusion contains 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 breast-feeding.
- If you are using any medicine known as an antiviral nucleoside (e.g. brivudine, sorivudine). These medicines are usually used to treat chickenpox and shingles.

Take special care with Ancotil

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.

Using other medicines

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 the medicine cytarabine (which is used to treat certain leukaemias), medicines to treat chickenpox or shingles (brivudine, sorivudine) or have used them in the last 4 weeks. These medicines may increase the possibility of unwanted effects with Ancotil. If you are taking medicines for epilepsy containing phenytoin, your doctor may do some blood tests.

Pregnancy and breast-feeding

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.
- You should not be given Ancotil if you are breast-feeding.

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.

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 to patients with kidney problems.

The treatment period with Ancotil will vary on a patient by patient basis, but treatment will not usually be longer than a week.

60018220G

Information for healthcare professionals

Ancotil® 2.5 g/250 ml (1 g 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.

Presentation

Infusion bottles containing 2.5 g flucytosine in 250 ml isotonic sodium chloride solution.

Other excipients are sodium chloride, tromethamine, hydrochloric acid and water for injections. The solution is colourless to slightly yellow.

Uses

Properties

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.

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. Elimination via peritoneal dialysis is possible.

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 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 long-standing 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.

Dosage and administration

Adults and children

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 and children 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.

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

In patients with:

creatinine clearance <40 to >20 ml/min: 50 mg/kg every 12 hours.

creatinine clearance <20 to >10 ml/min: 50 mg/kg every 24 hours.

creatinine clearance <10 ml/min: an initial single dose of 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.

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.

Neonates

The dose in neonates should be calculated in the same way as for adults and children, but the high possibility of renal impairment should be considered in this group either as intrinsic to their age or as a result of other nephrotoxic therapies. It is advised to closely monitor the serum levels of flucytosine in this group and adjust the dose according to levels. In cases where renal impairment is present the dose interval should be extended (as with adults and children). Where renal impairment is not a feature but serum levels are above those recommended, the dose should be reduced but the dosing intervals should remain the same.

Use in the 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.

Ancotil for Infusion is for intravenous or intraperitoneal administration.

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.

Contra-indications and warnings

Contra-indications

Ancotil is contra-indicated in patients who have shown hypersensitivity to flucytosine or any of the excipients and are being treated with antiviral nucleoside drugs (e.g. brivudine, sorivudine and their analogues). See Drug interactions section.

56UKIE1988105-01

Use in pregnancy and lactation

Teratogenic effects have been seen in rats. In this species flucytosine is metabolised to fluorouracil. The metabolism may differ in man: nevertheless, the use of Ancotil in pregnancy and in women of childbearing age requires that the potential benefits of therapy be weighed against its possible hazards. The drug should not be given to women, breast-feeding infants.

Precautions

The product should be used with great caution in patients with depression of bone marrow function or blood dyscrasias. Blood counts and tests of renal and hepatic function should be performed before and during treatment. This should occur at least weekly in patients with renal insufficiency or blood dyscrasias. Ancotil should not be used in patients with impaired renal function in the absence of facilities for monitoring blood levels of the drug. 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.

Flucytosine is metabolised to fluorouracil. Dihydropyrimidine dehydrogenase (DPD) is a key enzyme involved in the metabolism and elimination of fluorouracil. Therefore the risk of severe drug toxicity is increased when Ancotil is used in individuals with deficiency in 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.

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.

Side effects and adverse reactions

Nausea, vomiting, diarrhoea and skin rashes may occur but are usually of a transient nature. Less frequently observed side effects include allergic reactions, Lyell's Syndrome, myocardial toxicity and ventricular dysfunction, confusion, hallucinations, convulsions, headache, sedation and vertigo. Alterations in tests of liver function are generally dose-related and reversible but hepatitis and hepatic necrosis have been reported. Acute liver injury with possible fatal outcome in debilitated patients may occur in isolated cases. Haematological changes, mainly leucopenia, thrombocytopenia, agranulocytosis or aplastic anaemia have been reported. These are more common when serum levels of flucytosine are high in patients with renal impairment and when amphotericin-B has been co-prescribed. In isolated cases, bone marrow toxicity has been reported. This toxicity may be irreversible and could lead to death in patients with pre-existing immunosuppression. Local irritation or phlebitis does not appear to be a problem with Ancotil for Infusion.

Drug interactions

There is contradictory evidence concerning a drug interaction between Ancotil and 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.

Increased phenytoin plasma levels have been reported with concomitant administration of phenytoin and intravenous fluorouracil leading to symptoms of phenytoin intoxication. This is relevant to Ancotil as flucytosine is metabolised to fluorouracil. Patients receiving phenytoin and Ancotil concomitantly should be checked regularly for increased phenytoin plasma levels.

Treatment of overdosage

Haemodialysis produces a rapid fall in the serum concentration of Ancotil.

Pharmaceutical precautions

Storage

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.

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.

Additives

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. No other agent should be added to or mixed with Ancotil for Infusion.

Legal category

UK: POM

Ireland: Restricted to sale or supply on prescription only.

Package quantities

Ancotil for Infusion 2.5 g in 250 ml in packs of 5.

Further information

Availability

Ancotil for Infusion is available to hospitals only.

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.

Creatinine measurement

Flucytosine may interfere with the dual-slide 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.

Product Licence/Authorisation Numbers, Names and Addresses

Licence/Authorisation Numbers
UK: PL 15142/0002, Ireland: PA 1332/30/1, Malta: MA806/00801

The Product Licence/Authorisation holder is:
Meda Pharmaceuticals Ltd.,
Skyway House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK.

Meda Health Sales Ireland Limited,
Unit 34/35, Block A, Dunboyne Business Park, Dunboyne, Co. Meath, Ireland.

The manufacturer is:
Meda Pharma GmbH & Co. KG, Benzstrasse 1, 61352 Bad Homburg, Germany.

Date of last review

January 2014

MEDA

Ancotil can be given with a glucose and/or saline infusion. It should not be mixed in the same solution with other medicines.

4. POSSIBLE SIDE EFFECTS

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

Your doctor will monitor your reaction to Ancotil. Possible side effects include:

- Nausea, vomiting, diarrhoea and skin rashes may occur but these usually do not last long.

Less frequent side effects include:

- Allergic reaction. If you have an allergic reaction you may experience palpitations, swelling of eyelids, face, lips, mouth or tongue, sudden wheeziness, chest tightness, lumpy skin rash.
- Skin inflammation that may lead to severe blistering.
- Effects on the heart muscle and its pumping.
- Confusion, effects on your senses (e.g. seeing or hearing things), fits, headache, sleepiness and dizziness.
- Tests on your blood may show changes to your liver or certain factors in your blood.
- Ancotil contains 34.5 mmol (or 0.8 g) sodium/250 ml solution for infusion. To be be taken into consideration by patients on a controlled sodium diet.

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.

5. HOW ANCOTIL SOLUTION FOR INFUSION IS STORED

- All medicines should be kept out of the reach and sight 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

Meda Pharmaceuticals Ltd.,
Skyway House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK.

Meda Health Sales Ireland Limited.
Unit 34/35, Block A, Dunboyne Business Park, Dunboyne, Co. Meath, Ireland

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 November 2011.

MEDA

56UKIE1988105-01

0114_GI_Ancotil 250ml_56UKIE1988105-01.indd 3 14.01.14 17:09