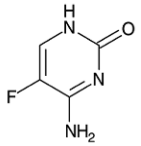
Product Information
ANCOTIL Injection for IV Infusion

NAME OF THE MEDICINE

Flucytosine



$C_4H_4FN_3O$

CAS number: 2022-85-7

DESCRIPTION

The active ingredient of Ancotil is 5-flucytosine (5-FC), a fluorinated pyrimidine. Ancotil is available as an isotonic infusion solution (1%) containing 0.805% sodium chloride. Ancotil also contains the excipients hydrochloric acid, trometamol and water for injections.

PHARMACOLOGY

Ancotil is effective *in vitro* and *in vivo* against certain species of fungi, particularly yeasts such as Candida species and *Cryptococcus neoformans* as well as against the pathogens of chromoblastomycosis.

The cells of sensitive pathogens can take up the active ingredient of Ancotil and, with the aid of specific cytosine deaminase, deaminate it to 5-fluorouracil. The amount of the latter incorporated into the ribonucleic acids of the pathogens is quantitatively related to the fungistatic activity. For many pathogens, the substance is also fungicidal on prolonged contact.

Of strains isolated in Europe from previously untreated patients, the majority (93% in the case of candidiasis and over 96% in the case of cryptococcosis) have proved sensitive to 5-FC. The minimum inhibitory concentration for these microorganisms is usually between 0.03 and 12.5 microgram per ml.

The development of resistance in initially sensitive strains has been observed during therapy with Ancotil. It is therefore recommended that sensitivity tests be performed before and also during treatment. It is essential to use antagonist-free media, such as those described by Scholer[1] and Shadomy[2]. The use of 5-FC discs is especially recommended. In several species of pathogens, mutual potentiation has been demonstrated *in vitro* and *in vivo* with a combination of Ancotil and amphotericin B. This was particularly pronounced in organisms with limited sensitivity to Ancotil.

PHARMACOKINETICS

Distribution: The volume of distribution is 0.78 $\pm$ 0.13 L per kg after intravenous administration.

The active ingredient of Ancotil does not become bound to serum protein. The concentrations in the CSF and peritoneal fluid amount to about 75% of the serum concentrations; in patients with normal kidney function the concentrations in the urine are always much higher than in the serum.

Elimination: The half life is three to six hours in adults with normal kidney function and six to seven hours in premature infants.

Since Ancotil is excreted by the kidneys almost exclusively as unchanged 5-flucytosine, impaired renal function results in prolongation of the half-life. It is essential that this fact be taken into account in determining the dosage (see *Special Dosage Instructions*).

Optimal active-ingredient concentration: The serum concentrations should be at least 20-25 micrograms per mL and transiently not more than 100-120 micrograms per mL. Prolonged concentrations of over 100 micrograms per mL must be avoided because of the increased risk of side effects.

INDICATIONS

Ancotil is indicated in the treatment of generalised candidiasis, cryptococcosis and chromoblastomycosis.

CONTRAINDICATIONS

Ancotil should not be administered to patients with known hypersensitivity to the medicine or any of the excipients.

PRECAUTIONS

Before and during treatment with Ancotil the patient's kidney function should be monitored, preferably by determination of endogenous creatinine clearance. If necessary, the dose should be adapted accordingly (See **Special Dosage Instructions**). Ancotil should not be used in patients with impaired renal function in the absence of facilities for monitoring blood levels of the drug.

Ancotil should be given with extreme caution to patients with bone marrow depression or blood dyscrasias. The blood picture, renal and liver function should also be monitored daily at the start of treatment and later twice weekly.

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.

Use in Pregnancy

Category B3.

Safety for use in pregnancy has not been established. Teratogenic effects have been seen in rats. Therefore, the drug is not recommended for use in pregnant women or those likely to become pregnant unless the expected benefit outweighs any potential risk.

Use in Lactation

It is not known whether flucytosine is excreted in breast milk. Therefore, it is not recommended for use in nursing mothers unless the expected benefits outweigh any potential risk.

INTERACTIONS WITH OTHER MEDICINES

Since there is a risk of leucopoenia (particularly neutropenia often accompanied by thrombocytopenia) when undergoing treatment with Ancotil, daily monitoring of the blood picture may be necessary where cytostatics are administered simultaneously.

Because excretion is almost exclusively renal, drugs which inhibit glomerular filtration automatically cause prolongation of the half-life of the active ingredient of Ancotil. In such cases it is essential that creatinine clearance be monitored regularly and the dose adapted accordingly.

The antimycotic effect of Ancotil is inhibited by the cytostatic cytosine arabinoside. Infusion solutions of Ancotil and amphotericin B should be administered separately.

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.

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.

ADVERSE EFFECTS

At the recommended dosage Ancotil is usually well tolerated. Nausea, vomiting, diarrhoea and skin rashes may occur. Allergic reactions, Lyell's syndrome, convulsions, headache, sedation, vertigo and myocardial toxicity and ventricular dysfunction have been reported ..

Haematological changes, mainly leucopenia, thrombocytopenia agranulocytosis or aplastic anaemia have been reported. In isolated cases, bone marrow toxicity has been reported. The toxicity may be irreversible and could lead to death in patients with pre-existing immunosuppression.

An increase of hepatic enzymes in the serum, hepatitis and hepatic necrosis have been reported Acute liver injury with possible fatal outcome in debilitated patients may occur in isolated cases.

Gastrointestinal bleeding (haemorrhage) has been observed when Ancotil was given in combination with amphotericin B and/or corticosteroids.

DOSAGE AND ADMINISTRATION

Intravenous administration of Ancotil using the infusion solution (37.5 - 50 mg per kg) is given as infusions of short duration (20 to 40 minutes). In patients whose renal function is normal, this dose is repeated at six hourly intervals.

Special Dosage Instructions: In patients with impaired renal function the interval between individual doses should be increased as follows:

Creatinine Clearance	Interval between single doses of 50 mg per kg bodyweight (maximum dose)
>40 mL per minute	6 hours
40 - 20 mL per minute	12 hours
20 -10 mL per minute	24 hours
<10 mL per minute	Determination of serum concentration of 5-FC 12 hours after the initial dose. Further doses are given as required in order to maintain serum concentration of between 25 and 50 micrograms/mL. (A method of determining 5-FC in biological fluids is described by Schoenebeck[3].)

Ancotil can be efficiently eliminated by both haemodialysis and peritoneal dialysis. With both methods, clearance is approximately as good as that of creatinine.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

No cases of intentional overdose are known. In cases of relative overdosage resulting from impaired renal function, there is an increased risk of undesirable effects both in incidence and severity in patients with a tendency to renal disorders (see **Adverse Effects**). These side affects are generally rapidly reversible on adjustment of the dosage or withdrawal of the drug.

PRESENTATION AND STORAGE CONDITIONS

Ancotil 2.5 g/250 mL (1% w/v) Injection comes in packs of 5 bottles.

Store below 25ºC

Precipitate occurs at prolonged storage below 15ºC. The precipitate can be redissolved by heating at a temperature of no higher than 80ºC for not longer than thirty minutes.

Storage above 25ºC may result in the formation of 5-fluorouracil, a cytostatic whose presence cannot be detected visibly.

Shelf Life: 18 months.

References

[1] Scholer H.J.: *Mykosen* (1970); 13, 179-188

[2] Shadomy S.: *Appl. Microbiol*. (1969); 17, 871-877

[3] Schoenebeck J. et.al: *Chemotherapy* (1973); 18, 321-336

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

15 March 1996.

DATE OF MOST RECENT AMENDMENT

5 September 2013