

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

ANCOTIL 500 mg, tablet

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flucytosine 500 mg  
Per tablet.

### 3. PHARMACEUTICAL FORM

Tablet.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic indications

Severe systemic fungal infections with susceptible pathogens, as an alternative or when switching from parenteral use, particularly: candidiasis, cryptococcosis, chromoblastomycosis and certain forms of aspergillosis.

Combination with another antifungal agent:

Flucytosine must be used in combination, in order to avoid as much as possible the selection of resistant mutations, especially in the treatment of candidiasis and cryptococcosis.

Combination with amphotericin B is often synergistic and never antagonistic.

#### 4.2. Posology and method of administration

Oral use.

##### Posology

Dosages range from 100 to 200 mg/kg per day, depending on the nature of the infection, its site and sensitivity of the causative agent.

The daily dosage must be divided into 3 or 4 oral doses.

##### USE IN PATIENTS WITH RENAL IMPAIRMENT

Doses must be administered at longer intervals, according to the following dosing regimen:

CREATININE CLEARANCE	SINGLE DOSE	INTERVAL
≥ 40 mL/min	25 to 50 mg/kg	6 hours
20 ≤ Cl < 40 mL/min	25 to 50 mg/kg	12 hours
10 ≤ Cl < 20 mL/min	25 to 50 mg/kg	24 hours
Cl < 10 mL/min	Single dose of 25 mg/kg, then plasma monitoring 12 hours after the initial dose, before repeating the dose.	

##### PATIENTS ON DIALYSIS

Since flucytosine is dialysable, the dose of this medicinal product must be repeated after each blood-cleansing session.

### COMBINATION WITH OTHER ANTIFUNGALS

The flucytosine/amphotericin B combination is synergistic: in some cases, it allows a dose reduction and reduces the risk of the emergence of secondary resistance to flucytosine.

There does not seem to be antagonism with imidazole derivatives.

#### **4.3. Contraindications**

Ancotil is contraindicated:

- in patients with known hypersensitivity to flucytosine or to any of the excipients.
- in combination with certain antiviral nucleosides such as brivudine, sorivudine and their analogues (irreversible inhibitors of dihydropyrimidine dehydrogenase (DPD) (see section 4.4 Special warnings and precautions for use).
- in breastfeeding women (see section 4.6 Fertility, Pregnancy and lactation).

#### **4.4. Special warnings and precautions for use**

Treatment with this medicinal product should be administered after identification of the strain and an assessment with regard to flucytosine susceptibility, due to possible primary resistance. It should be maintained under regular medical surveillance.

Ancotil tablets are not suitable for children under 6 years of age, who often have difficulty swallowing them due to their size. In this case, the tablets can be crushed to facilitate administration.

In patients with renal impairment, the dosage should be adjusted to creatinine clearance (see section 4.2).

65-75% of Ancotil present in the body is removed by haemodialysis. Therefore, in patients on dialysis, administration of this medicinal product must be repeated after each dialysis or blood-cleansing session.

It is recommended that blood counts and liver function tests be performed (ALAT, ASAT, alkaline phosphatases): regular monitoring especially at the start of treatment. As elimination of this medicinal product is exclusively renal, creatinine clearance must be regularly monitored in patients with renal impairment or in combination with a nephrotoxic agent likely to alter renal function, and the dosage must be adjusted according to this clearance (see section 4.2).

#### Contraception in men and women

Flucytosine is partially metabolised to 5-fluorouracil, which is genotoxic and considered to be potentially teratogenic in humans. Women of childbearing potential have to use effective contraception during treatment and up to 1 month after discontinuation of treatment. Male patients (or their female partners of childbearing potential) have to use effective contraception during treatment and up to 3 months after discontinuation of treatment (see section 4.6 Fertility, pregnancy and lactation).

#### **4.5. Interaction with other medicinal products and other forms of interaction**

##### Combinations requiring precautions for use

- Zidovudine

Increased haematological toxicity (additive myelotoxic effects). More frequent monitoring of blood counts.

In combination with a medicinal product with bone marrow or renal toxicity, more frequent monitoring of blood counts is recommended throughout the entire treatment, in view of the increased risk of haematological disorders (see section 4.8).

Influence on diagnostic tests: flucytosine may interfere in the enzymatic (2-step) creatinine assay, by causing an artificial elevation of the values observed.

#### **4.6. Fertility, pregnancy and lactation**

##### Contraception in men and women

Flucytosine is partially metabolised to 5-fluorouracil, which is genotoxic and considered to be potentially teratogenic in humans.

Women of childbearing potential have to use effective contraception during treatment and up to 1 month after discontinuation of treatment. Male patients (or their female partners of childbearing potential) have to use effective contraception during treatment and up to 3 months after discontinuation of treatment (see section 5.3 Preclinical safety data).

##### Pregnancy

Studies in animals have shown reproductive toxicity for flucytosine and one of its metabolites (5-fluorouracil) (teratogenicity and embryotoxicity) (see section 5.3 Preclinical safety data).

In humans, flucytosine crosses the placenta.

There are very limited data from the use of flucytosine in pregnant women.

Embryonic or foetal toxicity cannot be excluded, especially in the event of exposure during the first trimester. Therefore, Ancotil must not be used during pregnancy and in women of childbearing potential without effective contraception, unless absolutely necessary in case of life-threatening infections and in the absence of an effective therapeutic alternative.

If Ancotil is administered during pregnancy, the patient must be advised of the teratogenic risk with Ancotil and careful prenatal and postnatal monitoring must be performed. Furthermore, if administered up until delivery and in view of the safety profile of flucytosine, neonatal surveillance (haematological and hepatic) must be performed.

##### Breastfeeding

There are no data on the excretion of flucytosine in human milk.

Breastfeeding is contraindicated during treatment with flucytosine (see section 4.3 Contraindications).

#### **4.7. Effects on ability to drive and use machines**

Not relevant.

#### **4.8. Undesirable effects**

- Gastrointestinal disorders such as nausea, diarrhoea, more rarely vomiting.
- Haematological disorders: (leukopenia, thrombocytopenia), mainly moderate and transient and more common in patients with renal impairment or when serum flucytosine levels exceed 100 µg/mL. More severe disorders (aplasia, agranulocytosis), potentially irreversible and possibly

fatal in exception cases, have sometimes been observed; mainly, however, in patients undergoing treatment with bone marrow toxicity.

- Hepatic disorders: elevated transaminase levels (ASAT, ALAT), alkaline phosphatases, resolving upon discontinuation of treatment, as well as rare acute cases of hepatitis, have sometimes been observed.
- Cardiac disorders in exceptional cases, usually ischaemic in nature.
- Allergic manifestations: rare cases of skin rash and exceptional cases of Lyell's syndrome.

#### **4.9. Overdose**

In the event of overdose, which may result from impaired renal function in particular, exaggerated adverse reactions, especially haematological, can be expected. Blood counts must therefore be very closely monitored.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: antifungal for systemic use, ATC code: J: General anti-infectives for systemic use.

Activity: fungistatic in humans, at therapeutic doses.

Natural spectrum: *Candida albicans serotype A*, *Cryptococcus neoformans*, chromoblastomycosis agents and to a lesser extent: *Aspergillus*.

#### Mechanism of action

Cells of Ancotil-sensitive pathogens are able to absorb flucytosine (5-FC), which is subsequently metabolised to 5-fluorouracil (5-FU) via a specific cytosine deaminase. The amount of 5-FU incorporated into the ribonucleic acids of the pathogen is proportional to this same pathogen's susceptibility.

Possible resistance due to:

- Cases of primary resistance. Only via an *in vitro* study of the strain in question can its susceptibility be evaluated.
- Risk of acquired resistance during treatment. Combination with another antifungal is recommended.

Strains initially susceptible to Ancotil may acquire resistance during treatment. It is therefore recommended that the sensitivity of these strains be evaluated before and also during treatment. (The method described by Shadomy and Speller is well suited). Use of 5-FC discs is recommended.

For some pathogen species, synergy has been demonstrated *in vitro* and *in vivo* with a combination of Ancotil and amphotericin B, which is particularly pronounced in the case of organisms with reduced susceptibility to Ancotil.

#### **5.2. Pharmacokinetic properties**

##### Absorption

When administered orally, this treatment is absorbed by the digestive tract at a rate of 90% and produces the same concentrations as those observed following short-term IV infusion with an identical dose. After single IV administration, peak serum concentrations are approximately equivalent, in micrograms/mL, to the dose administered in mg/kg.

### Distribution

The volume of distribution is between 0.5 and 1 L/kg. This medicinal product is diffused throughout the body, including in the CSF, as a result of very low binding (< 5%) to plasma proteins.

Urinary concentrations of this medicinal product are always higher than plasma concentrations in patients with normal renal function.

### Metabolism

More than 90% of the flucytosine dose is recovered in unchanged form in the urine. Flucytosine is metabolised (probably by intestinal bacteria) to 5-fluorouracil (5-FU). The 5-FU/5-FC plasma concentration ratio is low.

### Elimination

The plasma half-life is 3 to 6 hours. Elimination is rapid via the kidneys, mainly by glomerular filtration, in unchanged form. In patients with renal impairment, the plasma half-life is prolonged; the dosage must therefore be adjusted to creatinine clearance (see section 4.2).

Flucytosine is dialysable.

### **5.3 Preclinical safety data**

*In vitro* studies on the mutagenic potential of flucytosine are negative. No studies are available on the carcinogenic potential of Ancotil.

Flucytosine is teratogenic and embryotoxic in rats receiving oral or parenteral doses of at least 40 mg/kg per day (240 mg/m<sup>2</sup> or 0.043 times the daily human dose).

5-fluorouracil, a metabolite of flucytosine, is genotoxic in mice and, *in vitro*, embryotoxic and teratogenic in mice and rats; it is classified as potentially teratogenic in humans. Malformations (abnormalities of the nervous system, palate, skeleton, tail and limbs) have occurred in several species (including rats and Syrian hamsters).

Embryotoxic effects (small foetus, resorption) have also been observed in monkeys treated with 5-fluorouracil.

Flucytosine and 5-fluorouracil cross the placental barrier.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Maize starch, microcrystalline cellulose, precipitated hydrated silica, polyvidone, magnesium stearate.

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

2 years.

### **6.4. Special precautions for storage**

Store below 25°C and protect from moisture.

**6.5. Nature and contents of container**

100 tablets in a bottle, closed by a polyethylene stopper.

**6.6. Special precautions for disposal and other handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

MEDA PHARMA  
40-44 RUE WASHINGTON  
75008 PARIS

**8. MARKETING AUTHORISATION NUMBER(S)**

317 964-3 or 34009 317 964 3 5: 100 tablets in a bottle.

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 January 1998

**10. DATE OF REVISION OF THE TEXT**

20 April 2017

**11. DOSIMETRY**

Not applicable.

**12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

Not applicable.