SUMMARY OF PRODUCT CHARACTERISTICS

OTYCULF 250 & 500
(Flucytosine Tablets 250 mg & 500 mg)

1. Name of The Medicinal Product

FLUCYTOSINE 250 mg,
tablet FLUCYTOSINE 500
mg, tablet

2. Qualitative and Quantitative Composition

Each tablet contains:
Flucytosine USP……. 250 mg

Each tablet contains:
Flucytosine USP……. 500 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Uncoated tablet

For 250 mg: “White to off-white round, flat faced round edge tablet debossed with **M** on one side and **FU1** on other side of the tablet”.

For 500 mg: White to off white, round flat faced round edge tablets debossed with "**M**" above the break line on one side of the tablet and "**FU2**" on the other side.

The tablet can be divided into equal halves.

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

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	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.

In anuric or nephrectomised patients on haemodialysis, the initial dose must not be repeated before the next dialysis session under any circumstances.

Hepatic impairment

The use of flucytosine has not been studied in patients with hepatic impairment.

Although hepatic impairment is not expected to have a significant effect on the pharmacokinetics of flucytosine, strict monitoring is necessary when treating with FLUCYTOSINE in patients with hepatic impairment. (See section 4.4 and section 5.2)

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.

Strict monitoring of renal function is necessary with this combination (see section 4.4).
There does not seem to be antagonism with imidazole derivatives.
Elderly

Since clinical data on the use of flucytosine in elderly patients are limited, this medicinal product may only be used in these patients if the expected benefit outweighs the potential risks.

Particular attention must be paid to renal function in this population.

Paediatric population

The available data are not sufficient to support evidence-based dosing recommendations in paediatric patients, including newborn and preterm infants.

Flucytosine must not be used as first-line treatment or monotherapy in paediatric patients. Flucytosine must be used in combination with other suitable antifungal agents, when other appropriate medicinal products are not available and are unlikely to be effective.

Method of administration

Oral use.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Lactation (see section 4.6).
Known dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4).

Combination with irreversible inhibitors of dihydropyrimidine dehydrogenase (DPD), such as brivudine, sorivudine and their analogues or uracil, a reversible DPD inhibitor, is contraindicated (see section 4.4).

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.

Flucytosine has a narrow therapeutic index and there is a risk of potential toxicity at high systemic concentrations.

The tablets are not suitable for children unable to swallow solid formulations.

Due to the prolonged elimination of flucytosine in paediatric patients, particularly in term and preterm newborns, administration of flucytosine may mean that optimal serum levels are exceeded. Monitoring of flucytosine plasma levels based on local (or national) guidelines for antifungal treatment and dose adjustments, if needed, are necessary to avoid excessive exposure to flucytosine.

Blood counts and renal function must be monitored regularly in paediatric patients during treatment, in order to monitor the creatinine concentration and its clearance.

Special monitoring

It is recommended that a blood count and liver function tests (ALT, AST, alkaline phosphatase) be performed prior to initiation of treatment, then regularly throughout it, especially during the initiation phase.

Patients with hepatic impairment may be treated with flucytosine but strict clinical and biological monitoring (AST, ALT, alkaline phosphatase) of liver function is required in conjunction with monitoring of plasma flucytosine levels. This medicinal product must be used with caution in patients with bone marrow suppression or blood dyscrasia, as well as in patients treated with immunosuppressive or cytostatic agents; due to a high risk of

haematological damage, strict clinical and biological monitoring (blood count) must be instituted, together with monitoring of plasma flucytosine levels.

Warnings with regard to renal function

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).

65-75% of Flucytosine 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.

Interference with biological measurements

Measurement of creatinine: Flucytosine can have an effect on the two-stage enzymatic measurement of creatinine levels and lead to false-positive diagnosis of azotaemia. Other methods are therefore recommended for measuring creatinine levels.

Dihydropyrimidine dehydrogenase deficiency (DPD)

Flucytosine is metabolised to fluorouracil.

Dihydropyrimidine dehydrogenase (DPD) is a key enzyme involved in the metabolism and elimination of fluorouracil.

The risk of systemic toxicity is increased when Flucytosine is used in patients with DPD deficiency.

Determination of DPD activity must be considered when systemic toxicity is confirmed or suspected.

When systemic toxicity is suspected, discontinuation of treatment must be considered.

An interval of 4 weeks minimum between treatment with sorivudine and other analogues that inhibit DPD, such as brivudine, must be observed prior to treatment with Flucytosine.

Monitoring plasma flucytosine levels during treatment:

Flucytosine levels must be monitored in order to adjust the dosage accordingly.
The mean steady-state serum level must be 35 to 70 µg/mL. The sensitivity of most sensitive strains *in vitro* is characterised by a minimum inhibitory concentration of between 10 and 25 µg/mL. However, values below 25 µg/mL must be avoided due to an increased risk of emerging resistance at low concentrations. Prolonged serum levels above 100 µg/mL must be avoided due to an increased risk of high haematological toxicity.

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).

Paediatric population:

Flucytosine has a narrow therapeutic index and there is a risk of potential toxicity at high systemic concentrations.

The tablets are not suitable for children unable to swallow solid formulations.

Due to the prolonged elimination of flucytosine in paediatric patients, particularly in term and preterm newborns, administration of flucytosine may mean that optimal serum levels are exceeded. Monitoring of flucytosine plasma levels based on local (or national) guidelines for antifungal treatment and dose adjustments, if needed, are necessary to avoid excessive exposure to flucytosine.

Blood counts and renal function must be monitored regularly in paediatric patients during treatment, in order to monitor the creatinine concentration and its clearance.

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

Contraindicated combinations (see section 4.3)

+ Antiviral antiherpetic nucleoside agents (e.g. brivudine, sorivudine and their analogues)

+ Uracil

Antiviral antiherpetic nucleoside agents (e.g. brivudine, sorivudine and their analogues) or uracil are potent inhibitors of dihydropyrimidine dehydrogenase (DPD), an enzyme that metabolises fluorouracil (see sections 4.4 and 4.5).

Since fluorouracil is a metabolite of flucytosine, combination of these medicines with Flucytosine is contraindicated (see section 4.3).

Combinations requiring precautions for use

+ Zidovudine

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

Combinations to be taken into account

+ Ganciclovir, valganciclovir

Increased haematological toxicity.

+ Cytotoxics

Increased haematological toxicity.

+ Immunosuppressants (ciclosporin, everolimus, sirolimus, tacrolimus, temsirolimus)

Increased haematological toxicity.

4.6. 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).

Pregnancy

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

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, Flucytosine 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 Flucytosine is administered during pregnancy, the patient must be advised of the teratogenic risk with Flucytosine 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).

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Gastrointestinal disorders:

Common: nausea, diarrhoea, vomiting, abdominal pain Not known: ulcerative colitis

Blood and lymphatic system disorders:

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.

Not known: eosinophilia

Hepatobiliary disorders:

Common: increased transaminase (AST, ALT) levels and alkaline phosphatase levels, regressing upon discontinuation of treatment.

Not known: acute hepatitis, hepatic cytolysis sometimes with fatal outcome

Cardiac disorders:

Not known: cardiac disorders usually of an ischaemic nature, myocardial toxicity, ventricular function disorders, cardiac arrest, tachycardia, arrhythmia

Immune system disorders:

Urticaria, hypersensitivity

Metabolism and nutrition disorders:

Not known: hypokalaemia.

Psychiatric disorders:

Not known: confusion, hallucinations

Nervous system disorders:

Not known: headache, sedation, convulsions, paraesthesias, peripheral neuropathy

Ear and labyrinth disorders:

Not known: vertigo

Respiratory and thoracic disorders:

Not known: dyspnoea, chest pain, respiratory arrest, acute respiratory insufficiency

Skin and subcutaneous tissue disorders:

Not known: pruritus, maculopapular erythema, photosensitivity reaction, Lyell's syndrome

Renal and urinary

disorders:

Not known: renal impairment, elevated serum creatinine and blood urea

General disorders and administration site conditions:

Not known: fever

Reporting of suspected adverse reactions

If you get any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet. If available, you can also report side effects directly through the national reporting system.

By reporting side effects, you can help provide more information on the safety of this medicine.

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 antiinfectives for systemic use.

Activity: fungistatic in humans, at therapeutic doses.

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

Mechanism of action

Cells of Flucytosine-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 Flucytosine 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 Flucytosine and amphotericin B, which is particularly pronounced in the case of organisms with reduced susceptibility to Flucytosine.

5.2. Pharmacokinetic properties

Absorption of Flucytosine 500 mg tablets:

The absorption characteristics of Flucytosine 500 mg tablet have been determined after administration of one Flucytosine 500 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value (±standard
Maximum concentration (C_{max})	12.379±2.647 µg/
Area under the curve ($AUC_{0-\infty}$), a measure of the	88.770±14.387
Time to attain maximum concentration (T_{max})*	1.00 (0.50-3.00)

* Median, Minimum and Maximum values reported for Tmax.

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.

Paediatric population:

Available data on the pharmacokinetics of flucytosine in paediatric patients are limited and suggest that the half-life of flucytosine is longer in children than in adults (4 vs. 7 h),

especially in newborns. A neonatal pharmacokinetic study demonstrated that the half-life of flucytosine was twice as long as in adults, even though peak concentrations were comparable. Furthermore, the volume of distribution of flucytosine approximates to the volume of total body water due to its high solubility. In a retrospective study with 391 paediatric patients, 65% of the mean concentrations of flucytosine exceeded the normal reference range.

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 Flucytosine.

Flucytosine is teratogenic and embryotoxic in rats receiving oral or parenteral doses of at least 40 mg/kg per day (240 mg/m2 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

Corn starch, povidone, partially pregelatinized maize starch, silicon dioxide, microcrystalline cellulose, magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5. Nature and contents of container HDPE Bottle

Pack size: 100 tablets

6.6. Special precautions for disposal <and other handling>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Mylan Laboratories
Limited Plot No.564/A/22
Road No.92, Jubilee Hills
Hyderabad, Telangana -
500096 India

8. Marketing Authorization Number

TAN 22 HM 0256

9. Date of first Authorization/Renewal of authorization

19th July, 2022

10. Date of Revision of this text