Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Flucytosine Tablets 500 mg

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Flucytosine Ph. Int. 500mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

White to off white, round, biconvex, beveled edge, uncoated tablets debossed with "K" and "24" separated by break-line on one side and plain on other side.
The tablet can be divided into two 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 clearance	Single dose	Interval
≥40 ml/min	25-50 mg/kg	6 hours

20≤Cl<40 ml/min	25-50 mg/kg	12 hours
10≤Cl<20 ml/min	25-50 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.

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. 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
- Lactation
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Combination with irreversible inhibitors of dihydropyrimidine dehydrogenase (DPD), such as brivudine, sorivudine and their analogues or uracil, a reversible DPD inhibitor, is contraindicated

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.

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.
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)
5-fluorouracil is a flucytosine metabolite. DPD is an enzyme that plays a key role in the metabolism and elimination of fluorouracil.
The risk of severe adverse reactions connected with the medicinal product is therefore increased when flucytosine is used in individuals with dihydropyrimidine dehydrogenase (DPD) deficiency. Determination of DPD activity can be considered when drug toxicity is confirmed or suspected.
In the case of suspected drug toxicity, consideration must be given to stopping flucytosine treatment. A minimum interval of 4 weeks must be observed between treatment with sorivudine and other DPD inhibitor analogues, such as brivudine, 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.

Paediatric population
Flucytosine has a narrow therapeutic index and there is a risk of potential toxicity at high systemic concentrations.
Due to the prolonged elimination of flucytosine in paediatric patients, particularly in term and pre-term newborns, administration of flucytosine may mean that optimal serum levels are exceeded.
Monitoring of plasma flucytosine 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.
The tablets are not suitable for children who are unable to swallow solid formulations.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

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.
Since fluorouracil is a metabolite of flucytosine, combination of these medicines with Flucytosine is contraindicated.

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

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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.

Pregnancy

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

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 exceptional 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: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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:J02AX01: Other antimycotics 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

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. Flucytosine is dialyzable.

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 /Maize starch, Povidone, Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide and Magnesium Stearate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

For container pack: Do not store above 30°C, Protect from moisture, Store in the original bottle tightly closed. Do not remove the desiccant.

6.5 Nature and Content of container

Container pack: 100's Tablet with silica gel
100 tablets packed in 120cc white, round, HDPE Container with 38mm Screw neck finish with 38mm Closure child resistant 123 white printed with heat seal liner with 1g Silica gel sachet and Polyester coil 12g/yard along with pack insert

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

Macleods Pharmaceuticals Ltd.
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Mumbai- 400 059, India

8. Marketing Authorization Number

CTD10098

9. Date of first authorization/renewal of the authorization

12/06/2024

10. Date of revision of the text

09/05/2024