PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

FLUCYTOSINE MYLAN 250 mg

FLUCYTOSINE MYLAN 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FLUCYTOSINE MYLAN 250 mg contains 250 mg flucytosine per tablet.

FLUCYTOSINE MYLAN 500 mg contains 500 mg flucytosine per tablet.

For full list of excipients, see section 6.1

Sugar free.

3 PHARMACEUTICAL FORM

Tablets.

FLUCYTOSINE MYLAN 250 mg:

White to off white round, flat faced round edge tablet debossed with **M** on one side and **FU1** on the other side of the tablet.

FLUCYTOSINE MYLAN 500 mg:

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FLUCYTOSINE MYLAN in combination with other antifungal medicines is indicated for treatment of severe systemic fungal infections caused by susceptible pathogens, by candidiasis, and cryptococcosis.

Combination with another antifungal medicine:

FLUCYTOSINE MYLAN 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.

4.2 Posology and method of administration

Posology:

Oral use: Dosages range from 100 to 200 mg/kg per day, depending on the nature of the infection, its site and sensitivity of the causative microorganism. The daily dosage must be divided into 3 or 4 oral doses.

A reduced starting dose should be considered to limit the risk of severe toxicity for patients with partial dihydropyrimidine dehydrogenase (DPD) deficiency (as they are at an increased risk of severe and potentially life-threatening toxicity). Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established *(see section 4.4).*

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 ≤ CrCl < 40 ml/min	25 to 50 mg/kg	12 hours
10 ≤ CrCl < 20 ml/min	25 to 50 mg/kg	24 hours
CrCl < 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 FLUCYTOSINE MYLAN 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 MYLAN 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.

Method of administration

Oral use.

4.3 Contraindications

FLUCYTOSINE MYLAN is contraindicated:

- in patients with known hypersensitivity to flucytosine or to any of the excipients (see section 6.1);
- in patients with a known dihydropyrimidine dehydrogenase (DPD) deficiency;
- in combination with irreversible inhibitors of dihydropyrimidine dehydrogenase (DPD), such as brivudine, sorivudine and their analogues or 5-fluorouracil and capecitabine, reversible DPD inhibitors (*see section 4.4*);
- in breastfeeding women (*see section 4.6*).

4.4 Special warnings and precautions for use

Treatment with FLUCYTOSINE MYLAN 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.

Caution is advised if flucytosine must be used in patients who are receiving treatment with Amphotericin B.

Patients receiving 5- fluorouracil and its prodrugs, capecitabine and tegafur, must be tested for dihydropyrimidine dehydrogenase (DPD) deficiency before starting treatment.

A reduced starting dose should be considered to limit the risk of severe toxicity for patients with partial dihydropyrimidine dehydrogenase (DPD) deficiency (as they are at an increased risk of severe and potentially life-threatening toxicity). Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established *(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)*.

4.5 Interaction with other medicines 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.

Contraindicated combinations (*see section 4.3*)

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

Uracil

Antiviral antiherpetic nucleoside medicines (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 MYLAN is contraindicated *(see section 4.3)*.

Amphotericin B

Concomitant use of amphotericin B may potentiate the toxicity of flucytosine. The exact mechanism of interaction is unknown. The risk of gastrointestinal, hepatic, and haematologic toxicity may be increased.

4.6 Fertility, pregnancy and lactation

Contraception in males and females:

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 MYLAN 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 MYLAN is administered during pregnancy, the patient must be advised of the teratogenic risk with FLUCYTOSINE MYLAN 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 MYLAN *(see section 4.3*).

4.7 Effects on ability to drive and use machines

FLUCYTOSINE MYLAN has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	(Leukopenia, thrombocytopenia), mainly moderate and transient and more frequent 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.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Cardiac disorders	Less frequent	Cardiac disorders in exceptional cases, usually ischaemic in nature. Myocardial toxicity, ventricular function disorders, cardiac arrest, tachycardia, dysrhythmia.
Gastrointestinal disorders	Less frequent	Nausea, diarrhoea, vomiting.
Hepato-biliary disorders	Less frequent	Acute hepatitis Elevated transaminase levels (AST, ALT), alkaline phosphatases, regressing upon discontinuation of treatment, as well as less frequent acute cases of hepatitis, have sometimes been observed.
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, maculopapular erythema, photosensitivity reaction, Lyell's syndrome.
Immune system disorders	Not known	Urticaria, hypersensitivity
Metabolism and nutrition disorders	Not known	Hypokalaemia

MedDRA system organ class	**Frequency**	**Adverse reactions**
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
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

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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 microorganisms 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. 5-fluorouracil incorporates itself into the RNA strand by competing with uracil, disrupting the RNA synthesis, and impairing protein synthesis within the fungus. 5-fluorouracil also further inhibits DNA synthesis by its conversion into fluoro-deoxyuridylic acid and inhibiting thymidylate synthase, which causes DNA damage within fungal cells. The enzyme cytosine deaminase is not present in mammalian cells, which is the understanding of its inactivity in bacteria and human cells.

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, flucytocine is completely 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. Flucytosine is diffused throughout the body, including in the CSF, as a result of very low binding (< 5 %) to plasma proteins.
Urinary concentrations of FLUCYTOSINE MYLAN 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 (within cells of intestinal flucytosine sensitive bacteria via a specific cytosine deaminase) to 5-fluorouracil (5-FU) the active metabolite. The 5-FU/5-FC plasma concentration ratio is low. The amount of 5-FU incorporated into the bacterial ribonucleic acids (RNAs) of the pathogen is proportional to this same pathogen's susceptibility to flucytosine.

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 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, active 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

Magnesium stearate

Maize starch

Microcrystalline cellulose

Povidone

Silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C and protect from moisture.

Keep the bottle tightly closed.

6.5 Nature and contents of container

FLUCYTOSINE MYLAN is presented in the following marketable packs:

HDPE Bottle Pack:

HDPE bottle pack comprises of round, wide mouth white high density polyethylene bottle with white opaque polypropylene screw cap closure with aluminium induction sealing liner wad with or without desiccant.

Pack size: 100 tablets per bottle.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando, 1600

Gauteng

Republic of South Africa

8 REGISTRATION NUMBER

FLUCYTOSINE MYLAN 250 mg: 54/20.2.2/0748

FLUCYTOSINE MYLAN 500 mg: 54/20.2.2/0749

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 December 2021

10 DATE OF REVISION OF THE TEXT

07 December 2021