WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

This patient information leaflet focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*] https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

Information for the patient

[HA754 trade name][†]
Flucytosine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have questions about the medicine, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness seem to be the same as yours.
- If you are concerned about any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [HA754 trade name] is and what it is used for

[HA754 trade name] is one of a group of medicines called antifungals and contains the active substance flucytosine.

[HA754 trade name] is used to treat certain serious systemic fungal infections, such as candidiasis, cryptococcosis, chromoblastomycosis and certain forms of aspergillus. It is usually used in combination with other medicines as an alternative to, or when switching from injectable medicines.

2. What you need to know before you take [HA754 trade name]

Posology:

The usual dose is between 100 to 150 mg/kg per day, depending on the nature of the infection, its site and sensitivity of the causative agent.

The daily dose 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 to < 40 mL/min	25 to 50 mg/kg	12 hours
10 to < 20 mL/min	25 to 50 mg/kg	24 hours
< 10 mL/min	Single dose of 25 mg/kg, then plasma monitoring 12 hours after the initial dose, before repeating the dose.	

Patients on haemodialysis:

Flucytosine is dialysable. Administration of flucytosine must be repeated after each dialysis session. Subsequent doses must not be administered before the next dialysis session under any circumstances.

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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 [HA754 trade name] in patients with hepatic impairment (see Sections 4.4 and 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.

Use in the elderly:

Since clinical data on the use of flucytosine in elderly patients are limited, [HA754 trade name] should 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 efficacy and safety of [HA754 trade name] have not been systematically studied in paediatric patients.

For adults, adolescents and children, a short course (one week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum of 800 mg daily) is recommended by the WHO as the preferred option for treating cryptococcal meningitis in individuals living with HIV.

3. How to take [HA754 trade name]

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breastfeeding (see Section 4.6).

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 (see Section 4.4).

4. Possible side effects

Treatment with [HA754 trade name] should be started after identification of the strain and an assessment for flucytosine susceptibility has been done, due to possible primary resistance. Ongoing treatment requires 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 for the duration of therapy, 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.

Patients with bone marrow suppression, blood dyscrasia or who are being treated with immunosuppressive or cytostatic agents require strict clinical and laboratory monitoring, due to a high risk of haematologic adverse events. This patient population also requires monitoring of plasma flucytosine levels.

Renal insufficiency:

As elimination of flucytosine is exclusively renal, creatinine clearance must be regularly monitored in patients with renal impairment or when the medicine is used 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).

Flucytosine is effectively removed by haemodialysis. Administration of [HA754 trade name] must be repeated after each dialysis 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 renal insufficiency. Other methods are therefore recommended for measuring creatinine levels.

Dihydropyrimidine dehydrogenase deficiency (DPD):

5-fluorouracil is a flucytosine metabolite. DPD 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 [HA754 trade name] 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 interrupting or stopping [HA754 trade name] 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 [HA754 trade name].

Monitoring plasma flucytosine levels during treatment:

Therapeutic drug monitoring (TDM) for flucytosine is considered a standard of care, based on well-established concentration toxicity relationships.

Mean steady-state serum concentrations of flucytosine should be in the range of 35 to 70 µg/mL

Trough concentrations should be between > 20-40 µg/mL. This range is based mainly on *in vitro* findings in which the emergence of drug resistance is observed when yeasts are exposed to lower concentrations. A peak concentration of 50-100 µg/dL is recommended to minimize hematological 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 must use effective contraception during treatment and up to 1 month after discontinuation of treatment. Male patients (or their female partners of childbearing potential) must 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.

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.

Reporting of side effects

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 improve understanding about the safety of this medicine.

5. How to store [HA754 trade name]

Do not store above 30ºC. Store in the original container.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the bottle after “EXP”. The expiry date refers to the last day of that month.

After first opening the bottle, tablets to be used within 100 days.

Do not throw away any medicines in wastewater or household waste. Ask your health care provider how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [HA754 trade name] contains

- The active ingredient is flucytosine. Each tablet contains 500 mg flucytosine.
- The other ingredients of [HA754 trade name] are: corn starch (maize starch), povidone, partially pregelatinized maize starch, silicon dioxide, microcrystalline cellulose, magnesium stearate.

What [HA754 trade name] looks like and contents of the pack

[HA754 trade name] is a white to off-white, round, flat-faced, round edge tablet debossed with 'M' above the break-line on one side of the tablet and 'FU2' on the other side.

The tablets are packed in a white, round HDPE bottle, closed with white opaque polypropylene screw cap with aluminium induction seal liner wad and white absorbent cotton fibre. Pack size: 100 tablets.

Supplier and Manufacturer

Supplier

Mylan Laboratories Limited
Plot No. 564/A/22
Road No. 92, Jubilee Hills
Hyderabad – 500096
Telangana
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E-mail: Imtiyaz.basade@viatris.com

Manufacturer

Mylan Laboratories Limited
Plot No. 11, 12 & 13 Indore Special Economic Zone
Pharma Zone, Phase – II, Sector – III
Pithampur – 454775, Dist. Dhar
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For any information about this medicine, contact the supplier.

This leaflet was last revised in November 2021

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines