WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics 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

1. NAME OF THE MEDICINAL PRODUCT

[HA754 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg flucytosine.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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 tablet can be divided into two equal doses.

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, to avoid as much as possible the selection of resistant organisms, 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:

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.

4.3 Contraindications

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).

4.4 Special warnings and precautions for use

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.

4.5 Interaction with other medicinal products and other forms of interaction

Drug combinations that are contraindicated (see Section 4.3):

- Antiviral nucleoside agents, such as brivudine, sorivudine and their analogues
- Uracil
- Fluorouracil

Antiviral nucleoside agents and uracil are potent inhibitors of dihydropyrimidine dehydrogenase (DPD), the key enzyme that metabolises fluorouracil (see Sections 4.4 and 4.5).

Since fluorouracil is a metabolite of flucytosine, its use in combination with [HA754 trade name] is contraindicated (see Section 4.3).

Combinations requiring precautions for use

- Zidovudine

Increased haematological toxicity (additive myelotoxic effects) is expected, requiring more frequent monitoring of blood counts.

Combinations requiring caution:

- Ganciclovir and valganciclovir

Increased haematological toxicity.

- Cytotoxic agents

Increased haematological toxicity.

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

Increased haematological toxicity.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential / 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 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 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).

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of flucytosine or [HA754 trade name] in pregnant women.

In humans, flucytosine crosses the placenta.

Embryonic or fetal toxicity cannot be excluded, especially in the event of exposure during the first trimester. Therefore, [HA754 trade name] 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 [HA754 trade name] is administered during pregnancy, the patient must be advised of the teratogenic risk with [HA754 trade name] 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. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flucytosine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Fertility

No data on the effect of [HA754 trade name] on fertility are available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA754 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events considered to be at least possibly related to treatment with flucytosine are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) or very rare (≤1/10,000). In addition, adverse events identified during post-approval use of flucytosine are listed (frequency category: 'not known'); however, since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been included for their potential causal connection to flucytosine, taking also into account their seriousness and the number of reports.

Gastrointestinal disorders:

Common: nausea, diarrhoea, vomiting, abdominal pain

Not known: ulcerative colitis

Blood and lymphatic system disorders

Common: leukopenia, thrombocytopenia (mainly moderate and transient: more common in patients with renal impairment or when flucytosine levels exceed 100 µg/mL)

Rare: marrow aplasia, agranulocytosis, potentially irreversible and possibly fatal in exceptional cases have been observed, mainly in patients undergoing treatment with concurrent agents causing bone marrow toxicity

Not known: eosinophilia

Hepatobiliary disorders

Common: increased transaminases (AST, ALT) and alkaline phosphatase, resolving upon treatment discontinuation

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

Cardiovascular disorders

Not known: cardiac arrest, myocardial toxicity, ventricular dysfunction

Immune system disorders

Not known: 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 reactions

Not known: fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

There is no experience with intentional overdosage. It is reasonable to expect that overdosage may produce pronounced manifestations of the known clinical adverse reactions. Prolonged serum concentrations in excess of 100 µg/mL may be associated with an increased incidence of toxicity, especially gastrointestinal (diarrhoea, nausea, vomiting), haematologic (leukopenia, thrombocytopenia) and hepatic (hepatitis).

In the management of overdosage, prompt gastric lavage or the use of an emetic is recommended. Adequate fluid intake should be maintained, by the intravenous route, if necessary, since [HA754 trade name] is excreted unchanged via the renal tract. The haematologic parameters should be monitored frequently; liver and kidney function should be carefully monitored, and appropriate management initiated as required.

Haemodialysis is effective in removing flucytosine and can be considered, particularly if there is significant renal insufficiency.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluorinated cytosine analogue antifungal for systemic use. ATC code: J02AX01.

Mechanism of action

The exact mode of action is unknown. Flucytosine penetrates fungal cells, where it is deaminated to fluorouracil by the fungal enzyme cytosine deaminase. Mammalian cells do not convert flucytosine to fluorouracil. Acting as an antimetabolite, fluorouracil competes with uracil, interfering with pyrimidine metabolism and eventually disrupting both RNA and protein synthesis. Flucytosine may also be converted to fluorodeoxyuridylic acid, which inhibits the enzyme thymidylate synthase and disrupts DNA synthesis. Although flucytosine is metabolized to 5-fluorouracil, flucytosine itself does not possess antineoplastic activity.

Susceptible fungi readily deaminate flucytosine to its active component, 5-fluorouracil. Resistance develops rapidly, however, if flucytosine is used as a single agent. The mechanism of resistance can be loss of the permease necessary for cytosine transport or decreased activity of uridine monophosphate pyrophosphorylase or cytosine deaminase.

Activity

Fungistatic in humans at therapeutic doses.

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

5.2 Pharmacokinetic properties

The absorption characteristics of [HA754 trade name] have been determined after administration of single tablets (containing 500 mg flucytosine) in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	12379 ± 2647 ng/ml
Area under the curve (AUC_{0-t}), a measure of the extent of absorption	82857 ± 13751 ng·h/ml

Time to attain maximum concentration (t_{max})	1.30 ± 0.61 h

Pharmacokinetics of flucytosine

Absorption	
Absolute bioavailability	Approximately 90 %
Food effect	Food decreases the rate of flucytosine absorption, but it does not impact the extent of absorption
Distribution	
Volume of distribution (mean)	0.5 to 1.0 L/kg
Plasma protein binding *in vitro*	< 5%
Tissue distribution	Widespread distribution, including into the CSF, vitreous and peritoneal fluids
Metabolism	
	Some metabolism (probably by intestinal bacteria) to 5-fluorouracil (5-FU). The 5-FU/flucytosine plasma concentration ratio is low. Minimal hepatic metabolism
Active metabolites	Converted to active 5-fluorouracil (5-FU) within susceptible fungal cells
Elimination	
Plasma half-life	3 to 6 hours.
% of dose excreted in urine	> 90%, mainly by glomerular filtration, as unchanged drug
% of dose excreted in faeces	Minimal
Drug interactions	
	5-FU metabolite levels may be increased due to inhibition of dihydropyrimidine dehydrogenase and in patients with deficiency of this enzyme.

Special populations

Renal impairment

Renal impairment reduces clearance, resulting in an increase in plasma half-life. Dosage must be adjusted based on creatinine clearance or eGFR

Flucytosine is removed by haemodialysis.

Hepatic impairment

Flucytosine is primarily eliminated by renal excretion and is not metabolized. Impaired hepatic function is not expected to influence the pharmacokinetics of flucytosine.

Pediatric patients

Limited data in paediatric patients suggest that the half-life is longer in children than in adults (4 vs. 7 hours) and particularly in newborn infants.

A neonatal PK study showed plasma half-life was twice as long as in adults, even though peak concentrations were comparable.

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

No studies are available on the carcinogenic potential of [HA754 trade name].

The mutagenic potential of flucytosine was evaluated in Ames-type studies with five different mutants of *S. typhimurium* and no mutagenicity was detected in the presence or absence of activating enzymes. Flucytosine was non-mutagenic in three different repair assay systems (i.e., rec, uvr and pol).

Flucytosine is teratogenic and embryotoxic in rats receiving oral or parenteral doses of at least 40 mg/kg per day (240 mg/m^2 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 fetus, 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

Partially pregelatinized maize starch

Silicon dioxide

Microcrystalline cellulose

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Tablets to be used within 100 days after first opening of the bottle.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA754

9. DATE OF PREQUALIFICATION

29 September 2021

10. DATE OF REVISION OF THE TEXT

November 2021

Section 6.3 updated in May 2023

References

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https://www.who.int/publications/i/item/9789241550277

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