

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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA769 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 500 mg flucytosine.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Uncoated tablets

White to off white, round, uncoated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have “K” and “24” debossed (stamped into) and separated by a break line on one side and are plain on the other side.

The break line can be used to divide [HA769 trade name] into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA769 trade name] is indicated together with other systemic antifungals in the treatment of susceptible severe or systemic fungal infections such as candidiasis, cryptococcosis (including cryptococcal meningitis), chromoblastomycosis and certain forms of aspergillosis. It is given for the oral continuation of parenteral treatment or as an alternative where the parenteral route is not appropriate.

Flucytosine must be used in combination, to minimise the selection of resistant organisms, especially in the treatment of candidiasis and cryptococcosis.

Treatment regimens should take into account the most recent official treatment guidelines (where available) and the susceptibility of the infection.

4.2 Posology and method of administration

Posology

The usual dose is between 50 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 4 oral doses.

The duration of treatment should be determined on an individual basis, depending on response. Typical treatment durations range between 2 to 4 weeks for systemic candidal infections to 6 to 12 months in patients with chromoblastomycosis. For a recommended short-course (1 week) regimen for cryptococcal meningitis in people living with HIV, see under ‘Special populations’, below.

Special populations

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

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

< 10 mL/min	Single dose of 25 mg/kg, then plasma monitoring 12 hours after the initial dose, before repeating the dose (typically every 48 hours).
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Patients on haemodialysis:

Flucytosine is dialysable. Typically, a dose of 25 to 50 mg per kg is given every 48 to 72 hours, after each dialysis session. Subsequent doses must not be administered 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 [HA769 trade name] in patients with hepatic impairment (see Sections 4.4 and 5.2).

Use in the elderly:

Clinical data on the use of flucytosine in elderly patients are limited.

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

Children

The efficacy and safety of [HA769 trade name] have not been systematically studied in paediatric patients (but see also 'People living with HIV', below).

People living with HIV

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 consolidation treatment with fluconazole, is recommended by the WHO as the preferred option for treating cryptococcal meningitis in individuals living with HIV.

Alternatively, a 2-week induction regimen comprising fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents) plus flucytosine 100 mg/kg/day divided into 4 daily doses may be used.

Combination with other antifungals

Antifungal synergism between flucytosine and polyene antibiotics, particularly amphotericin B, has been reported in vitro. [HA769 trade name] should always be given with other systemic antifungals to reduce the risk of the emergence of secondary resistance to flucytosine, and combination regimens with amphotericin B are widely used in order to take advantage of this synergistic effect. Strict monitoring of renal function is necessary with this combination (see section 4.4).

There does not seem to be antagonism with imidazole derivatives.

Method of administration

[HA769 trade name] is to be taken by mouth, with the daily dose divided and given in 4 parts. It can be taken with meals or on an empty stomach.

Where an individual dose is comprised of several tablets, patients may be advised to take them at intervals over a period of about 15 minutes, in order to reduce the risk of nausea and gastrointestinal disturbances.

4.3 Contraindications

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

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).

Use with fluorouracil or other prodrugs that are converted to fluorouracil

4.4 Special warnings and precautions for use

Treatment with [HA769 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.

Blood count and liver function tests (ALT, AST, alkaline phosphatase) are recommended before starting treatment, then regularly for the duration of therapy, especially during the initiation phase. Renal function may also need to be monitored (see 'Renal insufficiency', below).

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 receiving immunosuppressive or cytostatic treatments 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.

Monitoring plasma flucytosine levels during treatment

Where available, therapeutic drug monitoring (TDM) for flucytosine may be appropriate as standard of care in some situations, particularly 48 to 72 hours after starting therapy, after dose adjustment or beginning or starting concomitant treatment with other medicines that may interact, and if there is evidence of toxicity.

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

Trough concentrations measured just before the next dose should be at least 25 µg/mL, as lower levels may be associated with the development of resistance. A peak concentration of less than 100 µg/mL measured 2 hours post-dose is recommended to minimise toxicity.

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 can have an effect on the two-stage enzymatic measurement of creatinine levels and lead to false-positive diagnosis of renal insufficiency. Other methods (e.g. Jaffé reaction) are therefore recommended for measuring creatinine levels.

Flucytosine is effectively removed by haemodialysis. Administration of [HA769 trade name] must be repeated after each dialysis session (see section 4.2).

Dihydropyrimidine dehydrogenase deficiency (DPD)

Although mammalian cells (unlike fungal cells) do not take up flucytosine and metabolise it to fluorouracil, some flucytosine is converted to fluorouracil in the body, probably by intestinal flora. 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 [HA769 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 [HA769 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 [HA769 trade name].

Use in children

Elimination may be more prolonged and exposure therefore greater in children, especially younger children. Flucytosine has a narrow therapeutic index and so there is a risk of potential toxicity at high systemic concentrations.

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

[HA769 trade name] is not suitable for patients such as very young children who are unable to swallow the tablets whole.

4.5 Interaction with other medicinal products and other forms of interaction

Use of [HA769 trade name] with inhibitors of dihydropyrimidine dehydrogenase (DPD) is **contraindicated**. These include the nucleoside antivirals brivudine, sorivudine and analogues, and the reversible DPD inhibitor uracil (see also section 4.3). Use with the combination tegafur/gimeracil/oteracil, which contains a prodrug of fluorouracil (tegafur) and a reversible DPD inhibitor (gimeracil) should also be avoided.

An interval of at least four weeks should elapse between treatment with brivudine, sorivudine or analogues and subsequent administration of [HA769 trade name]. An interval of at least 7 days should be observed between taking tegafur/gimeracil/oteracil and subsequent use of [HA769 trade name].

Since fluorouracil is a metabolite of flucytosine, its use in combination with [HA769 trade name] is also contraindicated (see Section 4.3).

Care is required if [HA769 trade name] is used with other myelosuppressants, or with medicines that may reduce renal function (glomerular filtration) and thus lead to increased flucytosine exposure. Increased monitoring of blood counts and renal function respectively is recommended.

The following table includes some of the interactions expected with flucytosine:

Drugs (grouped by therapeutic area)	Interaction	Recommendation on co-administration
ANTIVIRALS		
HIV antiretrovirals		
<i>Nucleoside/nucleotide transcriptase inhibitors</i>		
Emtricitabine	Potential increased haematological toxicity	Careful monitoring of blood counts is recommended. Consider dose reduction if required.
Lamivudine		
Tenofovir disoproxil	Potential increased haematological and renal toxicity	Careful monitoring of blood counts and creatinine is advised; consider dose reduction if required.
Zidovudine		
Other antivirals		
Brivudine Sorivudine	Irreversible inhibition of DPD: Flucytosine C_{max} ↑ $t_{1/2}$ ↑	Concomitant use is contraindicated; allow at least 4 weeks after cessation of the antiviral regimen before beginning flucytosine treatment
Ganciclovir Valganciclovir	Potential increased haematological toxicity	Careful monitoring of blood counts is recommended.
ANTIPILEPTICS		
Phenytoin	Potential for increased phenytoin concentrations leading to phenytoin toxicity	Increased phenytoin plasma levels have been reported with concomitant administration of phenytoin and intravenous fluorouracil; since flucytosine is metabolised to fluorouracil the potential exists for increased plasma concentrations of phenytoin if the two are co-administered and patients should be monitored appropriately.

ANTINEOPLASTICS		
Capecitabine	Prodrug of fluorouracil; additive toxicity expected	Since capecitabine is converted to fluorouracil in the body, use with flucytosine should be avoided
Cytarabine	Reduced antifungal activity (due to competitive inhibition) has been reported	Strict monitoring of blood levels and clinical progress is required if the two medicines are given concurrently
Fluorouracil	Active metabolite of flucytosine; additive toxicity expected	Concomitant use is contraindicated
Tegafur/gimeracil/oteracil	Additive toxicity expected	Concomitant use is contraindicated
IMMUNOSUPPRESSANTS		
Ciclosporin Everolimus Sirolimus Tacrolimus Temsirolimus	Potential increased haematological toxicity	Careful monitoring of blood counts is recommended.
↓	Decreased	AUC area under the curve (bioavailability)
↑	Increased	C _{max} maximum (peak) concentration (in plasma or blood)
↔	No change	C _{min} minimum (trough) concentration (in plasma or blood)

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 for 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 [HA769 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, [HA769 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 [HA769 trade name] is administered during pregnancy, the patient must be advised of the teratogenic risk with [HA769 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, but there is potential for serious adverse reactions in nursing infants from flucytosine and therefore breastfeeding is usually considered to be

contraindicated. Where necessary, 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 [HA769 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 [HA769 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) or very rare ($\leq 1/10,000$). 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 $\mu\text{g/mL}$)

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, paraesthesia, 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

Common: rash

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

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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 may be considered. Adequate fluid intake should be maintained, by the intravenous route, if necessary, since [HA769 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 symptomatic 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

Flucytosine is a fluorinated pyrimidine derivative. It is an antimycotic agent exerting fungistatic and fungicidal activity by interfering with protein and DNA synthesis. Fungal cells absorb flucytosine selectively via cytosine permease. It is desaminated to 5-fluorouracil which is then incorporated into fungal RNA, leading to faulty protein biosynthesis. 5-Fluorouracil is also converted to fluorodeoxyuridine monophosphate by uracil phosphoribosyltransferase (UPRTase). Fluorodeoxyuridine interferes with the enzyme thymidylate synthase. Inhibition of thymidylate synthase subsequently causes disruption of DNA synthesis.

Although flucytosine is metabolized to 5-fluorouracil, flucytosine itself does not possess antineoplastic activity.

Activity

Flucytosine has fungistatic and fungicidal activity in systemic and local infections against yeasts such as *Candida*, *Torulopsis* and *Cryptococcus* as well as in chromoblastomycosis. In *Aspergillus*, it shows exclusively fungistatic activity.

An in-vitro study on susceptibility of approximately 8,800 clinical isolates (yeasts and filamentous fungi) to flucytosine according to NCCLS (The National Committee for Clinical Laboratory Standards) guidelines demonstrated that the four most common *Candida* species are extremely sensitive (the minimal inhibitory concentration for *Candida* species varied from 0.12 µg/ml to 1 µg/ml for 90% of the tested strains).

Resistance

Two major mechanisms of resistance have been described:

- decreased activity of the cytosine permease or deaminase, leading to a decreased uptake or conversion of the drug. This mechanism is responsible for primary and intrinsic resistance.

- loss of activity of UPRTase.

Resistance may also result from increased synthesis of pyrimidines, which compete with the fluorinated antimetabolites of 5-FC and thus diminish its antimycotic activity. Other mechanisms of flucytosine resistance include the up-regulated expression of a vacuolar glutathione S-conjugate pump that pumps flucytosine out of cells as well as the induced expression of a multi-drug resistance gene that permeates flucytosine out of cells.

Primary resistance has been observed in some fungi. However, it occurs only very rarely with *Candida* spp. (95% susceptible, 2% intermediary, 3% resistant), except for *C. krusei* (5% susceptible, 67% intermediary, 28% resistant), while resistance is common in *C. lusitaniae*. Intermediately susceptible or resistant strains are also not uncommon in *C. tropicalis*.

Resistance in *Cryptococcus neoformans* is rare but around 30 % of strains show intermediate susceptibility.

Secondary resistance may develop, in particular with flucytosine monotherapy. Strains initially susceptible to flucytosine may become resistant during therapy. It is thus recommended to estimate the susceptibility of the strains before and during therapy.

Combination of flucytosine and other antimycotic agents such as amphotericin B and triazoles often result in a synergistic effect; the MIC value achieved with the combination is less than the MIC values of the individual substances.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA769 trade name] have been determined after administration of tablets of [HA769 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value ± standard deviation arithmetic mean ± SD
Maximum concentration (C _{max}) ng/mL	11410 ± 1545
Area under the curve (AUC _{0-∞}), a measure of the extent of absorption ng.hour/mL	85405 ± 10646
Time to attain maximum concentration (t _{max}) hour	1.38 ± 0.61

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 <i>in vitro</i>	< 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.

Children

Limited data in paediatric patients suggest that the half-life of flucytosine is longer in children than in adults (4 vs. 7 hours) and particularly in newborn infants (however, [HA769 trade name] is not suitable for use in children who cannot swallow tablets).

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 [HA769 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/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 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

maize starch

povidone

microcrystalline cellulose

crospovidone

colloidal silicon dioxide

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. Protect from moisture. Avoid excursions above 30°C.

6.5 Nature and contents of container

Strip pack

Plain aluminium foil (laminated with polyethylene film) strip packs, each containing 6 tablets. Available in cartons of 14×6 tablets.

HDPE bottle

Round, opaque white plastic (HDPE) bottle containing 100 tablets. It contains a sachet of desiccant (drying material) and a piece of polyester coil to keep the tablets in place. The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

No special requirements

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA769

9. DATE OF PREQUALIFICATION

25 April 2024

10. DATE OF REVISION OF THE TEXT

June 2024

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Detailed information on this medicine is available on the World Health Organization (WHO) website: <https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>