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

[MA058 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of artesunate and 270 mg of amodiaquine (as hydrochloride).
For a full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

[MA058 Trade Name] is a round bilayer tablet : one layer is yellow coloured, the other one is white to slightly yellow, with score line, engraved on one side “AS” and on the other side “100”.
The tablets may be mottled but it does not alter the safety and effectiveness of the product.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA058 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and to artesunate.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with [MA058 trade name].

[MA058 trade name] should not be used in regions where amodiaquine resistance is widespread because such use significantly increases the risk of developing resistance to artesunate.

4.2 Posology and method of administration

The doses of [MA058 trade name] are shown below (in terms of tablets as well as the active substances). Information is given for all weights of patients in whom the tablets can be used. However, it is important to ensure that the pack size, i.e. the number of tablets in the pack, is sufficient for the full treatment course according to the child's weight.

Patient’s weight (approximate age)	**Dose**	
18–36 kg (6–13 years)	1 tablet daily for 3 days	amodiaquine 270 mg + artesunate 100 mg daily for 3 days
more than 36 kg (over 14 years)	2 tablets daily for 3 days;	amodiaquine 540 mg + artesunate 200 mg daily for 3 days

The dosage of [MA058 trade name] is based on the following weight-based doses of the two components:

- amodiaquine 10 mg/kg daily for 3 days

- artesunate 4 mg/kg daily for 3 days.

Administration

[MA058 trade name] is taken orally and the tablets should be swallowed with water. They should not be taken with a meal that contains a high amount of fat (see section 5.2).

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

For patients unable to swallow the tablets, e.g. very young children, the tablets can be crushed and either mixed in water or taken with water.

If the patient vomits within half an hour after dosing, another dose of [MA058 trade name] should be taken. In case of further vomiting, treatment for severe malaria should be considered.

Renal and hepatic impairment

No data are available on dosing in patients with hepatic or renal impairment (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients
- History of liver injury during treatment with amodiaquine
- Previous haematological event during treatment with amodiaquine
- Retinopathy (in case of frequent treatment)

[MA058 trade name] must not be used for malaria prophylaxis since it may result in agranulocytosis and severe hepatotoxicity (see section 4.4).

4.4 Special warnings and precautions for use

[MA058 trade name] should not be used in regions where amodiaquine resistance is widespread, as treatment with the combination may mean effectively a treatment with artesunate alone with an insufficient duration and lower plasma concentrations as compared to treatment with artesunate alone (see section 4.5). As a result, the risk of *P. falciparum* developing resistance to artesunate increases significantly.

Amodiaquine is effective against some chloroquine-resistant strains of *P. falciparum*, although there is cross-resistance.

[MA058 trade name] has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

[MA058 trade name] has not been evaluated in the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale* and is therefore not recommended.

[MA058 trade name] has not been evaluated for malaria prophylaxis. The use of amodiaquine for prophylaxis results in an unacceptably high risk of agranulocytosis and liver toxicity and is contraindicated. Therefore, the combination of amodiaquine and artesunate is also contraindicated for malaria prophylaxis.

[MA058 trade name] has not been studied in patients with thalassaemia, sickle cell anaemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

In the absence of specific clinical studies, caution should be exercised in patients with renal or hepatic impairment.

Symptoms suggestive of the following diseases should be carefully monitored:

- hepatitis, pre-icteric phase and especially when jaundice has developed,
- agranulocytosis (as suggested, for instance, by a clinical condition including fever, tonsillitis or mouth ulcers).

When these symptoms develop or worsen during treatment with [MA058 trade name], laboratory tests are required at once for liver function, or blood cell counts, or both. Immediate discontinuation of treatment may be required since continuation of treatment with amodiaquine increases the risk of death.

Cardiovascular effects have been reported with 4-aminoquinoline derivatives. Due to a potential for QT prolongation, amodiaquine should be used with caution in patients with: cardiac disease, a history of ventricular dysrhythmias, uncorrected hypokalaemia or hypomagnesaemia, or bradycardia (< 50 beats per minute), and during concomitant use of substances that prolong the QT interval (see Sections 4.5).

The combination of artesunate and amodiaquine may induce neutropenia and increase the risk of infection.

Acute extrapyramidal side effects may occur with [MA058 trade name], even after a single dose (see section 4.8). These reactions usually resolve after discontinuing treatment with [MA058 trade name] and medical treatment of the neurological condition. Alternative antimalarial therapy should be instituted.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions may occur with drugs used for treating HIV and tuberculosis, though few clinical data are available. Prescribers should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia. Concomitant administration of [MA058 trade name] and efavirenz should be avoided, since this combination can cause marked hepatotoxicity.

Concomitant administration is not recommended of [MA058 trade name] with drugs that inhibit the liver enzymes cytochrome (CYP) 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) or those that inhibit CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast).

No pharmacokinetic interactions of artesunate with other important antimalarial drugs have been identified. However, concomitant administration of [MA058 trade name] with other antimalarial treatments is not recommended, as data on efficacy and safety are not available.

The concentration of dihydroartemisinin (DHA, the main active metabolite of artesunate), decreases when artesunate and amodiaquine are used concomitantly (C_{max} decreased 47%, $AUC_{0-\infty}$ decreased 17%).

Agranulocytosis and hepatitis have occurred after long-term use of amodiaquine for prophylaxis. Therefore, caution should be observed when [MA058 trade name] is used concurrently with other drugs that cause liver or haematological toxicity.

Amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some beta-blockers, antidepressants, and antipsychotics drugs. Caution should be exercised when they are co-administered with [MA058 trade name].

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Malaria is particularly hazardous during pregnancy. The healthcare provider must consider the benefits and risks of treatment with [MA058 trade name] for the mother and the fetus.

The safety of amodiaquine in pregnant women has not been formally established, but many years of experience with it does not indicate a risk of teratogenicity.

Data on a limited number of exposed pregnant women do not indicate any adverse effect of artemisinins on pregnancy or on the health of the baby. Animal data indicate a limited embryotoxic effect at daily doses of 6 mg/kg or more.

During first trimester of pregnancy, [MA058 trade name] should not be used unless clearly necessary e.g. if treatment is life-saving for the mother and if another antimalarial is not suitable or is not tolerated.

During second and third trimesters, [MA058 trade name] may be used with caution, only if other antimalarials cannot be used.

Breastfeeding

The amounts of antimalarials in breast milk are small. Therefore, lactating women can receive [MA058 trade name] for malaria treatment.

4.7 Effects on ability to drive and use machines

Patients receiving [MA058 trade name] should be warned that somnolence, dizziness or asthenia may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

The safety of amodiaquine/artesunate was evaluated through two comparative pivotal studies involving 1003 patients treated with the fixed dose combination.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Most of the adverse reactions observed in clinical studies were similar to symptoms usually seen during a malaria attack. The most frequent adverse reactions were anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough (see hereafter).

The most serious adverse reactions observed in these pivotal studies were asthenia, anaemia and vertigo.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from available data).

Infections and infestations	
Uncommon	bronchitis acute, gastroenteritis, oral candidiasis
Immune system disorders	
Unknown frequency	allergic reaction*
Blood and lymphatic system disorders	
Uncommon	anaemia
Unknown frequency	leucopenia**, neutropenia (agranulocytosis), sometimes severe**
Metabolism and nutrition disorders	
Uncommon	hypoglycaemia
Psychiatric disorders	
Common	anorexia, insomnia
Uncommon	hallucination
Nervous system disorders	
Common	somnolence
Uncommon	paraesthesia
Rare	neuromyopathy**
Unknown frequency	extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis) *, headache*, dizziness*, convulsions*
Eye disorders	
Uncommon	ocular icterus
Very rare	irreversible retinopathy (requiring specialist ophthalmic care)**
Unknown frequency	transient accommodation disorders**, corneal opacity (reduces on stopping treatment)**
Ear and labyrinth disorders	
Uncommon	vertigo
Cardiac disorders	
Common	prolonged QT interval (frequency based on studies in 289 patients with ECG recording) *
Uncommon	arrhythmia, bradycardia
Respiratory, thoracic, and mediastinal disorders	
Common	cough

Gastro-intestinal disorders

Common	nausea, abdominal pain
Uncommon	diarrhoea, vomiting

Hepatobiliary disorders

Unknown frequency	severe hepatitis (sometimes fatal)[**], splenomegaly[*], jaundice*

Skin and subcutaneous tissue disorders

Uncommon	pruritus, rash, face oedema, skin disorders
Unknown frequency	slate-grey pigmentation (notably affecting fingers and mucous membranes)[**]

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia

General disorders and administration site conditions

Common	asthenia
Uncommon	oedema peripheral, pyrexia
Unknown frequency	cold[*], flu[*], rhinitis[*], shivering[*], sore throat[*]

[*] Data from post-marketing experience
[**] Reported in HIV-infected patients, particularly in those on zidovudine and/or cotrimoxazole. Also reported with amodiaquine alone, especially at higher doses and/or during prolonged treatment

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

In case of suspected overdose, the patient should be urgently transferred to a specialist unit with facilities for clinical monitoring and where symptomatic and supportive therapy can be given.

Amodiaquine

The dose at which amodiaquine can cause serious toxicity is not known; by comparison with chloroquine, it can be estimated at around 2 g as a single dose in adults,

Symptoms and signs: headache, dizziness, visual disorders, QT interval prolongation, cardiovascular collapse and convulsions, followed by respiratory and cardiac arrest. Extrapyramidal disorders have been reported.

Artesunate

There is limited experience of overdose with artesunate. Artesunate overdose should be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Artesunate Amodiaquine Combination (ATC code P01BF03)

[MA058 trade name] is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different biochemical targets in the parasites.

Artesunate: Artesunate is a derivative of dihydroartemisinin, which is obtained from artemisinin extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (*Artemisia annua*).

In vitro artemisinin derivatives are active against a broad spectrum of the life cycle of the *Plasmodium falciparum* parasite, from the relatively inactive ring stage to late schizonts. The schizonticidal and gametocytocidal activities of orally administered artesunate have been demonstrated in vivo on chloroquine-sensitive strains of Plasmodium (*P. berghei* in mice and *P. knowlesi* in monkeys) and on chloroquine-resistant strains (*P. berghei* in mice).

Artesunate appears to be inactive against extra-erythrocyte forms, sporozoites, liver schizontes or merozoites.

When administered orally, artesunate consistently acts more quickly than orally administered chloroquine and intravenous quinine in all animal models studied, regardless of the strain or dose tested. In macaques (the animal model most similar to humans) infection with a chloroquine-resistant strain of *P. knowlesi* was cured with the same doses of artesunate and quinine.

Amodiaquine: Amodiaquine is a synthetic 4-aminoquinoline antimalarial. It has schizonticidal action on *P. falciparum, P. vivax, P. ovale* and *P. malaria* which destroys intraerythrocytic forms.

The mechanism of action of 4-aminoquinoline derivatives against plasmodium has not been established. Amodiaquine can penetrate the infected red blood cells and prevent the parasite from polymerizing haeme into an insoluble product called haemozoin, leading to parasite death.

Strains of *Plasmodium falciparum* resistant to 4-aminoquinolines (chloroquine, amodiaquine) are present in many areas, and their geographical distribution is constantly changing. However, amodiaquine remains active against some chloroquine-resistant *P. falciparum* strains.

Clinical efficacy and safety

[MA058 trade name] is for use in areas where parasite resistance to amodiaquine remains low.

Efficacy and safety of [MA058 trade name] in uncomplicated *P. falciparum* malaria have been demonstrated in clinical trials in various settings in Africa. Trials also suggest adequate efficacy in south-east Asia and Latin America.

Efficacy and safety in children and adults

The efficacy and safety of [MA058 trade name] in uncomplicated *P. falciparum* malaria were demonstrated in two pivotal studies (Burkina-Faso study and ATAQ-EASY multinational study) in children and adults, as well as in 13 other supportive studies.

A randomised, controlled, open-label, parallel-group study in Burkina-Faso compared the efficacy and safety of [MA058 trade name] tablets to an almost equivalent regimen of the individual drugs given together in 750 children aged 6 months to 5 years. The parasitological cure rates after 28 days were the same (92%) in both groups. Analysis of both clinical and parasitological data demonstrated the non-inferiority of the artesunate and amodiaquine combination compared to separate drugs used concomitantly.

A multinational, randomised, blinded, comparative study (ATAQ EASY) of the efficacy and safety of [MA058 trade name] tablets vs artemether/lumefantrine tablets in the treatment of uncomplicated *P. falciparum* malaria was conducted in 4 African countries (Cameroon, Madagascar, Mali and Senegal) in 941 adults and children.

Adequate clinical and parasitological cure rates in the intention-to-treat (ITT) population on day 28 were 95.2% with artesunate/amodiaquine fixed-dose combination once a day (n = 310) and 95.5% with the artemether/lumefantrine twice daily group (n = 311). In children aged less than 5 years, in the ITT population on day 28 cure rates were 94.4% in the artesunate/amodiaquine group (n = 143) and 93.7 % in the artemether/lumefantrine group (n = 142). The clinical and parasitological efficacy of artesunate/amodiaquine combination was non-inferior to artemether/lumefantrine.

Efficacy and safety in infants and children treated for repeated malaria attacks

A 2-year, randomised, single-centre, open study, compared the efficacy of the [MA058 trade name] tablets and artemether/lumefantrine tablets in uncomplicated *P. falciparum* malaria in Uganda in 416 children aged from 6 to 59 months for treating repeated malaria attacks. Over this 2-year period, a total of 6033 episodes were monitored.

The 28-day parasitological cure rate was 97.5 % for artesunate/amodiaquine vs 97.0 % for artemether/lumefantrine for the first attack and cure rates for over 100 subsequent malaria episodes ranged from 88.1% to 98.9 % per episode, with no clear difference between the treatment arms.

Cure rates remained stable in both treatment groups over time during the 23 months of the study.

A 3-day course of [MA058 trade name] was non-inferior to artemether/lumefantrine in children aged less than 5 years presenting with a first episode of uncomplicated *Plasmodium falciparum* malaria.

Repeated use of artesunate/amodiaquine and artemether/lumefantrine between 2 to 26 times (median: 15 times) over a 2-year period in this study did not reveal unexpected safety issues. Safety profiles for both were good and comparable, and there was no evidence of emerging toxicity due to repeated use.

Serious adverse events per malaria attack over the first 23 episodes ranged from 0 to 2% with artesunate/amodiaquine vs 0 to 0.6% with artemether/lumefantrine. Only one serious event in each group was considered to be related to treatment. In both cases, increases in hepatic enzymes were reported and patients recovered spontaneously.

5.2 Pharmacokinetic properties

The absorption characteristics of [MA058 trade name] have been determined after administration of two tablets (i.e. 200mg artesunate and 540mg amodiaquine) of [MA058 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** (*)	
	Artesunate	**Amodiaquine**
Maximum concentration (C_{max}) ng/ml	162.9	9.2
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.hour/ml	89.9	65.7
Time to attain maximum concentration (t_{max}) hour (median (range))	0.25 (0.25 – 1.33)	0.79 (0.48 – 8)

*geometric mean

Pharmacokinetics of artesunate and amodiaquine

	Artesunate	**Amodiaquine**
General		
C_{max} ng/mL	162.9	9.2
$AUC_{0-\infty}$ ng·hour/mL	89.9	65.7
t_{max} hours (median (range))	0.25 (0.25-1.33)	0.79 (0.48-8)
Absorption		
Absolute bioavailability		The absolute bioavailability of amodiaquine is not known.
Oral bioavailability	Absorption is rapid. Most of the artesunate is promptly biotransformed to the active metabolite dihydroartemisinin (DHA)	Amodiaquine is quickly absorbed and biotransformed to its main active form, desethylamodiaquine.
Food effect	When [MA056] was taken with a high fat meal in healthy volunteers, the C_{max} and $AUC_{(0-t)}$ of artesunate decreased 66% and 13% respectively, compared to fasting.	When [MA056] was taken with a high fat meal in healthy volunteers, the C_{max} and $AUC_{(0-t)}$ of amodiaquine increased 23% and

	The C_{max} and $AUC_{(0-t)}$ of the active metabolite (DHA) decreased 48% and 5% respectively with a high-fat meal, compared to fasting.	58% respectively, compared to fasting. The C_{max} and $AUC_{(0-t)}$ of the active metabolite desethylamodiaquine increased 18% and 12% respectively with a high-fat meal, compared to fasting.
Distribution		
Volume of distribution		Amodiaquine: 20–40 L/kg Desethylamodiaquine, the main metabolite of amodiaquine, is found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4-6 times higher than in plasma.
Plasma protein binding *in vitro*	Artesunate is not significantly protein-bound	
Tissue distribution	Active metabolite, DHA, accumulates substantially in P. faliciparum-infected erythrocytes	
Metabolism		
	Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. Its main metabolite, DHA is presumed to account for most of the in vivo antimalarial activity. DHA is further metabolised through glucuronidation before excretion.	The hepatic metabolism of amodiaquine, through the isoenzyme CYP2C8, is high, with formation of the active metabolite, desethylamodiaquine
Elimination		
Plasma half-life	3–29 minutes (artesunate) 40–95 minutes (DHA)	Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is eliminated with a terminal half-life of 9–18 days.

Special populations

For the combined use of artesunate and amodiaquine, no pharmacokinetic data are available for patients with impaired renal or hepatic function.

5.3 Preclinical safety data

General toxicity

Artesunate presents low acute toxicity. After repeated doses of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. 5 and 8.25 times the maximal therapeutic dose in humans, it is potentially toxic to the haematopoietic organs, the immune system and response, the liver and kidneys.

For *amodiaquine* pigmentation was seen in the heart at 30 mg/kg/day in rats. The statistically significant inn vitro effects on ion channels in the heart at 0.1 μM in the hERG current (expressed in human embryonic kidney cells) as well as the increase in QRS complex and QT interval durations at concentrations higher than 0.1 μM in the isolated rabbit Purkinje fibres appeared to be due to a non-specific multi-ion channel blockade. Pigmentation was also seen in liver, kidney and thyroid glands in rats as well as in kidneys, liver and lymph

nodes in dogs (at doses of 25 mg/kg/day). Also, haemosiderosis increased in the spleen and bone marrow and thymus lymphoid depletion occurred.

Toxicity after acute and chronic administration of the combination artesunate/amodiaquine was similar to that with artesunate and amodiaquine, given alone. In repeated-dose toxicity studies, the incidence and the severity of lesions was generally related to the dose levels. Amodiaquine given alone at 30 mg/kg/day induced effects very similar to those of the 12/30 mg/kg/day artesunate/amodiaquine combination.

Genotoxicity

In vitro and in vivo tests (Ames, mouse micronucleus) did not reveal any mutagenic or clastogenic potential of artesunate. Although amodiaquine, like chloroquine, has both mutagenic and clastogenic potential, studies with the artesunate/amodiaquine combination in the Ames test and micronucleus in rat did not demonstrate genotoxicity.

Carcinogenesis

No studies of the carcinogenic potential of the combination of artesunate and amodiaquine or the individual agents have been conducted.

Toxicity to reproduction

Reproductive toxicology studies in rats and rabbits have confirmed the embryotoxic and teratogenic potential of artesunate and the maternal toxicity associated with amodiaquine. The combination did not demonstrate any particular effects on fertility or associated parameters. In the peri-postnatal study, the offspring from the F1 generation did not show any effect on sexual development, and despite early slowing of bodyweight increase with some effect on testicular and epididymal weights, no sequelae were noted on reproductive capacity.

No new toxicity was induced through the administration of the two substances in combination.

Safety pharmacology

Slight sedative effect, decreased body temperature, a slight natriuretic effect and decreased endogenous creatinine clearance were observed with *artesunate* after single intravenous doses of 200 mg/kg (mice), 450 mg (rats, rabbits and dogs) and after single oral doses of 180 mg/kg in male rats. In conscious telemetered dogs, atrio-ventricular blocks and depressant effects on smooth muscles were reported with a single oral dose of 10 mg/kg. Since these effects were observed only in female animals, at a low incidence and without relation to dose, the relationship to artesunate administration cannot be confirmed. Neither neurotoxicity nor prolongation of QT(c) interval were shown.

Amodiaquine is likely to induce cardiovascular adverse effects, particularly transient prolongation of QT interval with an oral dose of 30 mg/kg. This dose level corresponds to approximately 2-fold the maximum recommended therapeutic dose. Also, slight respiratory depressant and natriuretic effects occurred with an oral dose of 100 mg/kg (about 6.7-fold the maximum therapeutic dose).

Oral administration of *amodiaquine followed by artesunate* was safe for the central nervous, cardiovascular and respiratory systems at dose levels of artesunate and amodiaquine corresponding to approximately 1.67-fold and 1.81-fold the maximum therapeutic dose (15/5.5 mg/kg amodiaquine/artesunate). The natriuretic effect on the kidney was very slight and transient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Croscarmellose sodium
- Povidone K30
- Silicon colloidal anhydrous
- Microcrystalline cellulose
- Magnesium stearate
- Calcium carbonate DC CS90 (calcium carbonate and maize starch)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
The product should be stored below 30°C in the original package.

6.5 Nature and contents of container
3 tablets packaged in an aluminium/aluminium blister pack.
6 tablets packaged in an aluminium/aluminium blister pack
Box containing 1 or 25 blisters per pack.

6.6 Instructions for use and handling and disposal
Not applicable

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)
MA058

9. DATE OF PREQUALIFICATION
14 October 2008

10. DATE OF REVISION OF THE TEXT
October 2021

Reference list

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