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

[MA177 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg dihydroartemisinin and 320 mg piperaquine phosphate.

Excipients with potential clinical effect

Each film-coated tablet contains 0.17 mg FD&C yellow #6/sunset yellow FCF aluminium lake.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'D•C' debossed (stamped into) one side and a break line on the other side.

The break line can be used to divide [MA177 trade name] into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA177 trade name] is indicated for the treatment of uncomplicated malaria. [MA177 trade name] is active against all *Plasmodium* parasites that cause malaria in humans.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

4.2 Posology and method of administration

Posology

[MA177 trade name] should be administered over 3 consecutive days for a total of 3 doses taken at the same time each day.

Dosing should be based on body weight as shown in the following table:

Body weight	Number of tablets	Daily dose	
		Dihydroartemisinin	Piperaquine phosphate
11 kg to less than 17 kg	1 tablet per day for 3 days	40 mg	320 mg
17 kg to less than 25 kg	1½ tablets per day for 3 days	60 mg	480 mg
25 kg to less than 36 kg	2 tablets per day for 3 days	80 mg	640 mg
36 kg to less than 60 kg	3 tablets per day for 3 days	120 mg	960 mg
60 kg to less than 80 kg	4 tablets per day for 3 days	160 mg	1280 mg
80 kg or more	5 tablets per day for 3 days	200 mg	1600 mg

For patients weighing less than 11kg, alternative formulations supplying lower amounts of active substance should be preferred.

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

Dispersible formulations may be preferred in children if available.

When supplying this product to the patient, it is important to ensure that the pack size, i.e. the number of tablets supplied, is sufficient for a full treatment course according to the patient's weight.

Missed dose

If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed.

Vomiting after administration

- If a patient vomits within 30 minutes of taking [MA177 trade name], the whole dose should be re-administered.
- if a patient vomits within 30-60 minutes of administration, half the dose should be re-administered.

Re-dosing with [MA177 trade name] should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be started.

Repeated courses

There are no data on a second course of treatment.

No more than 2 courses of [MA177 trade name] may be given within a 12-month period (see sections 4.4 and 5.3).

A second course of [MA177 trade name] should not be given within 2 months after the first course due to the long elimination half-life of piperaquine (see sections 4.4 and 5.2).

Special populations

Elderly

Clinical studies of dihydroartemisinin/piperaquine did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders (see sections 4.3 and 4.4), caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment

Dihydroartemisinin/piperaquine has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering [MA177 trade name] to these patients (see section 4.4).

Method of administration

[MA177 trade name] should be taken orally with water and without food (high-fat meals can alter absorption of piperaquine):

- Each dose should be taken no less than 3 hours after the last food intake.
- No food should be taken within 3 hours after each dose.

For patients unable to swallow the tablets, [MA177 trade name] may be crushed and mixed with water. The mixture should be swallowed immediately after preparation.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe malaria according to WHO definition.
- Inherited long QT syndrome (congenital prolongation of the QTc interval) or a family history of this condition or of sudden death.
- Any other clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.

- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
  - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
  - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive medicinal products.
  - Certain antimicrobial medicinal products, including medicinal products of the following classes:
    - macrolides (e.g. erythromycin, clarithromycin),
    - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
    - imidazole and triazole antifungal medicinal products,
    - pentamidine and saquinavir.
  - Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
  - Droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that [MA177 trade name] is started, taking into account their elimination half-life (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial medicinal products).

4.4 Special warnings and precautions for use

[MA177 trade name] should not be used to treat complicated malaria.

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another antimalarial agent is started due to treatment failure or a new malaria infection (see below). In addition, piperaquine is an inhibitor and substrate of CYP3A4 and caution is needed if given with other medicinal products that affect or are metabolised via this system (see section 4.5).

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than 2 courses of [MA177 trade name] should be given in a 12-month period (see section 5.3).

Effects on cardiac repolarisation

In clinical trials with dihydroartemisinin/piperaquine limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with dihydroartemisinin/piperaquine therapy than with the comparators (see section 5.1 for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in dihydroartemisinin/piperaquine-treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of dihydroartemisinin/piperaquine, in one of the two Phase III studies 3 out of 767 patients (0.4%) were reported to have a QTcF value of >500 milliseconds (ms) versus none in the comparator group.

The WHO guidelines no longer recommend performing an ECG before prescribing dihydroartemisinin/piperaquine. However, dihydroartemisinin/piperaquine should not be used in patients with known congenital long QT interval syndromes or those who have a clinical condition or are taking a medication that prolongs the QT interval.

There has been no evidence of piperaquine-related cardiotoxicity in large, randomised trials or in extensive deployment in the field.

Delayed haemolytic anaemia

Delayed haemolytic anaemia has been observed up to 1 month following use of intravenous artesunate and oral artemisinin-based combination treatment (ACT), including dihydroartemisinin/piperaquine. Some cases have been severe and required blood transfusion. Risk factors may include young age (children under 5 years old) and previous treatment with IV artesunate.

Patients and caregivers should be advised to be vigilant for signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness and confusion.

Furthermore, some patients with delayed haemolytic anaemia after dihydroartemisinin/piperaquine treatment show evidence of autoimmune haemolytic anaemia. Therefore, if available, a direct antiglobulin test (Coombs test) should be considered to determine whether treatment, e.g. with corticosteroids, is needed.

Paediatric population

Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of [MA177 trade name].

Hepatic and renal impairment

Dihydroartemisinin/piperaquine has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if [MA177 trade name] is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

Excipients

[MA177 trade name] contains FD&C yellow #6/sunset yellow FCF aluminium lake which may cause allergic reaction.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

[MA177 trade name] is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval, due to the risk of an additive effect on the QTc interval (see section 4.3).

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering [MA177 trade name] with *other medicines metabolised via CYP3A4*, as the therapeutic and/or toxic effects of some co administered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) has been noted when given with *strong CYP3A4 inhibitors*, resulting in a potential exacerbation of the effect on QTc prolongation (see below). Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4 inhibitors should be discouraged after initiation (i.e. the first dose) of [MA177 trade name] (see section 5.2).

Exposure to piperaquine may also be increased when co-administered with *mild or moderate CYP3A4 inhibitors* (e.g. oral contraceptives). Therefore, caution should be applied when co-administering [MA177 trade name] with any CYP3A4-inhibitor and ECG monitoring should be considered.

A limited number of drug-drug pharmacokinetic interaction studies with [MA177 trade name] have been performed in healthy adult subjects. The assessment of the potential for drug-drug interactions to occur is therefore based on either *in vivo* or *in vitro* studies.

Effect of [MA177 trade name] on co-administered medicinal products

The concurrent administration of oral [MA177 trade name] with 7.5 mg oral *midazolam*, a CYP3A4 probe substrate, led to a modest increase (≤2-fold) in midazolam and its metabolites exposure in healthy adult subjects. This inhibitory effect was no longer evident 1 week after last administration of [MA177 trade name]. Therefore, particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. *antiretroviral medicinal products* and *ciclosporin*) are co-administered with [MA177 trade name].

From *in vitro* data, piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as *omeprazole*, with consequent increase of their plasma concentration, and therefore, of their toxicity.

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as *paracetamol* or *theophylline*, and the anaesthetic gases *enflurane, halothane* and *isoflurane*. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

When co-administered to healthy women, [MA177 trade name] exerted only a minimum effect on an estrogen/progestogenic combination *oral contraceptive treatment*, increasing the rate of absorption of ethinylestradiol (expressed by geometric mean C_{max}) by about 28% but not significantly changing the exposure to ethinylestradiol and levonorgestrel and not influencing contraceptive activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant [MA177 trade name] administration. For the possible need for ECG monitoring if the two medicines are given together, see above.

Dihydroartemisinin administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when [MA177 trade name] is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as *theophylline*. Any effects are unlikely to persist beyond 24 hours after the last intake of dihydroartemisinin.

Effect of co-administered medicinal products on [MA177 trade name]

Piperaquine is metabolised by CYP3A4 *in vitro.* The concurrent administration of a single dose of oral *clarithromycin* (a strong CYP3A4 inhibitor probe) with a single dose of oral [MA177 trade name] led to a modest increase (≤2-fold) in piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination may result in an exacerbation of the effect on QTc. Therefore, particular caution is required if [MA177 trade name] is administered to patients taking potent CYP3A4 inhibitors (e.g. some *protease inhibitors* [amprenavir, atazanavir, indinavir, nelfinavir, ritonavir], *nefazodone* or *verapamil*), and ECG monitoring should be considered due to the risk of higher plasma concentrations of piperaquine.

Enzyme-inducing medicinal products such as *rifampicin*, *carbamazepine, phenytoin, phenobarbital, St. John's wort* (*Hypericum perforatum*) are likely to lead to reduced piperaquine plasma concentrations. The concentration of dihydroartemisinin may also be reduced. Concomitant treatment with such medicinal products is not recommended.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The interactions documented above for adults should be considered for the paediatric population.

Food interaction

Absorption of piperaquine is increased in the presence of fatty food (see section 5.2) which may increase its effect on QTc interval. Therefore, [MA177 trade name] should be taken with water only, as described in section 4.2. [MA177 trade name] should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[MA177 trade name] may be used during the first trimester of pregnancy when the first-line option (artemether-lumefantrine) is not suitable or available. [MA177 trade name] can be used during the second and third trimester of pregnancy.

There are limited data on the use of dihydroartemisinin and piperaquine in pregnant women, particularly in the first trimester. Animal data has suggested a potential for birth defects and teratogenicity when dihydroartemisinin and piperaquine are administered during the first trimester of pregnancy (see section 5.3).

However, a meta-analysis of all exposures to artemisinin-based treatment (ABT) in the first trimester of pregnancy showed no differences between pregnancies exposed in the first trimester to artemisinin and those exposed to non-ABT in terms of the composite adverse pregnancy outcome (ABT=42/736 [5.7%] vs non-ABT=96/1074 [8.9%]; aHR: 0.71; 95% CI: 0.49–1.03). Analysis for adverse pregnancy outcomes against the individual parameters in the composite analysis, including miscarriage, stillbirth or congenital anomalies, also revealed no statistically significant difference. There was also no difference in the risk of these adverse pregnancy outcomes when exposures were restricted to the putative embryo-sensitive period. This analysis strengthens previous findings that the potential for artemisinin-based embryotoxicity observed in animal studies is not reflected in humans treated for malaria although few exposures in the first trimester of pregnancy can be documented.

Dihydroartemisinin piperaquine phosphate was used successfully in the second and third trimesters of pregnancy in more than 2000 women on the Myanmar–Thailand border for rescue therapy and in Indonesia for first-line treatment. WHO guidelines consider that experience with artemisinin derivatives in the second and third trimesters (over 4000 documented pregnancies) is increasingly reassuring.

Breastfeeding

Animal data suggest excretion of piperaquine into breast milk, but the amounts that enter breast milk and are consumed by breastfeeding infants are expected to be relatively small. In line with WHO guidelines, [MA177 trade name] can be used in breastfeeding women.

Fertility

There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Data obtained in animal studies show that fertility is unaffected by dihydroartemisinin in both females and males.

4.7 Effects on ability to drive and use machines

[MA177 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

Summary of the safety profile

The safety of dihydroartemisinin/piperaquine has been evaluated in 2 phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients over 18 years treated with dihydroartemisinin/piperaquine.

In a randomised trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to dihydroartemisinin/piperaquine, 25% of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥5%.

The most frequent ADRs observed at an incidence ≥1.0% were: headache (3.9%), electrocardiogram QTc prolonged (3.4%), *P. falciparum* infection (3.0%), anaemia (2.8%), eosinophilia (1.7%), haemoglobin decreased (1.7%), sinus tachycardia (1.7%), asthenia (1.6%), haematocrit [decreased] (1.6%), pyrexia (1.5%), red blood cell count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.

In a second randomised trial, 1,038 children, aged between 6 months and 5 years, were exposed to dihydroartemisinin/piperaquine and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: cough (32%), pyrexia (22.4%), influenza (16.0%), *P. falciparum* infection (14.1%), diarrhoea (9.4%), vomiting (5.5%) and anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs in the study.

The ADRs noted for dihydroartemisinin/piperaquine in these trials were generally mild in severity, and the majority were non-serious. Reactions such as cough, pyrexia, headache, *P. falciparum* infection, anaemia,

asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria.

Tabulated list of adverse reactions

The undesirable effects of dihydroartemisinin/piperaquine are listed below by body system or organ. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

ADRs in adult patients participating in clinical studies with dihydroartemisinin/piperaquine and post-marketing data:

Infections and infestations	
Common	*P. falciparum* infection
Uncommon	respiratory tract infection; influenza
Blood and lymphatic disorders	
Common	anaemia
Not known	autoimmune haemolytic anaemia, delayed haemolytic anaemia
Metabolic and nutrition disorders	
Uncommon	anorexia
Nervous system disorders	
Common	headache
Uncommon	convulsion; dizziness
Cardiac disorders	
Common	QTc interval prolongation; tachycardia
Uncommon	cardiac conduction disorders; sinus arrhythmia; bradycardia
Respiratory disorders	
Uncommon	cough
Gastrointestinal disorders	
Uncommon	vomiting; diarrhoea; nausea; abdominal pain
Hepatobiliary disorders	
Uncommon	hepatitis; hepatocellular injury, hepatomegaly; abnormal liver function tests
Skin and subcutaneous tissue disorders	
Uncommon	pruritis
Musculoskeletal and connective tissue disorders	
Uncommon	arthralgia; myalgia
General disorders and administration site conditions	
Common	asthenia; pyrexia

Description of selected adverse reactions

The effect on prolongation of the QTc interval was observed on Day 2 and had resolved by Day 7 (the next time point at which ECGs were performed).

Paediatric population

A tabular overview of the frequency of the ADRs in paediatric patients is given below. The majority of paediatric experience is derived from African children aged 6 months to 5 years.

ADRs in paediatric patients participating in clinical studies with dihydroartemisinin/piperaquine and post-marketing data:

Infections and infestations

Very common	influenza; *P. falciparum* infection
Common	respiratory tract infection; ear infection

Blood and lymphatic disorders

Common	thrombocytopenia; leukopenia/neutropenia; leukocytosis; anaemia
Uncommon	thrombocytosis; splenomegaly; lymphadenopathy; hypochromasia
Not known	autoimmune haemolytic anaemia, delayed haemolytic anaemia

Metabolic and nutrition disorders

Common	anorexia

Nervous system disorders

Uncommon	convulsion; headache

Eye disorders

Common	conjunctivitis

Cardiac disorders

Common	QTc interval prolongation; irregular heart rate
Uncommon	cardiac conduction disorders; cardiac murmur

Respiratory disorders

Very common	cough
Uncommon	rhinorrhoea; epistaxis

Gastrointestinal disorders

Common	vomiting; diarrhoea; abdominal pain
Uncommon	stomatitis; nausea

Hepatobiliary disorders

Uncommon	hepatitis; hepatomegaly; abnormal liver function tests; jaundice

Skin and subcutaneous tissue disorders

Common	dermatitis; rash
Uncommon	acanthosis; pruritis

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia

General disorders and administration site conditions

Very common	pyrexia
Common	asthenia

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

In clinical trials, 9 patients received double the cumulative intended dose of dihydroartemisinin/piperaquine. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, antimalarials, artemisinin and derivatives, combinations, ATC code: P01BF05

Pharmacodynamic effects

Dihydroartemisinin is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:

- Inhibition of *falciparum* sarcoplasmic-endoplasmic reticulum calcium ATPase
- Interference with mitochondrial electron transport
- Interference with parasite transport proteins
- Disruption of parasite mitochondrial function

The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haem (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinolone, and this class has shown good antimalarial activity against chloroquine-resistant *Plasmodium* strains *in vitro*. The bulky bisquinolone structure may be important for activity against chloroquine-resistant strains, and may act through the following mechanisms:

- Inhibition of the transporters that efflux chloroquine from the parasite food vacuole
- Inhibition of haem-digestion pathway in the parasite food vacuole

Resistance to piperaquine (when used as monotherapy) has been reported.

The efficacy and safety of dihydroartemisinin/piperaquine have been assessed in two large randomised, open-label clinical trials:

Study DM040010 was conducted in Asian adult and paediatric patients with uncomplicated *P. falciparum* malaria. Dihydroartemisinin/piperaquine (DHA/PPQ) treatment was compared with Artesunate + Mefloquine (AS + MQ). The primary endpoint was the PCR-corrected cure rate at Day 63.

Study DM040011 was conducted in African paediatric patients with uncomplicated *P. falciparum* malaria. Dihydroartemisinin/piperaquine (DHA/PPQ) treatment was compared with Artemether + Lumefantrine (A + L). The primary endpoint was PCR-corrected cure rate at Day 28.

The results for the primary endpoint in the modified intent to treat (m-ITT) populations (defined as all randomised patients who received at least one dose of the study treatment, with the exclusion of those patients lost to follow up for unknown reasons) were as follows:

Study	PCR-corrected cure rate (m-ITT)			
	DHA/PPQ	**AS+MQ**	**A+L**	**95 % two-sided CI on the treatment difference (DHA/PPQ - Comparator)**
DM040010 (n=1087)	97.0%	95.3%	-	(-0.84, 4.19) %; p=0.161
DM040011 (n=1524)	92.7%	-	94.8%	(-4.59, 0.45) %; p=0.128

In each case the results confirmed that DHA/PPQ was not inferior to the comparator medicinal product. In both studies, the true treatment failure rate was below the 5% efficacy threshold set by WHO.

The age-specific PCR-corrected cure rates in the m-ITT populations are tabulated below for the Asian and African studies, respectively:

Study	PCR-corrected cure rate (m-ITT)			
	DHA/PPQ	**AS+MQ**	**A+L**	**95 % two-sided CI on the treatment difference (**DHA/PPQ **- Comparator)**
DM04010 (n=1087)				
≤5 years	100.0%	100.0%	-	-
>5 to ≤12 years	98.2%	96.5%	-	(-3.67, 7.09) %; p=0.605
>12 to ≤18 years	97.3%	100.0%	-	(-6.40, 0.99) %; p=1.000
>18 to ≤64 years	96.6%	94.4%	-	(-0.98, 5.30) %; p=0.146
DM04011 (n=1524)				
≤1 year	91.5%	-	98.5%	(-12.66, -1.32) %[(1)]; p=0.064
>1 to ≤2 years	92.6%	-	94.6%	(-6.76, 2.63) %; p=0.413
>2 to ≤5 years	93.0%	-	94.0%	(-4.41, 2.47) %; p=0.590

[(1)] This CI is asymptotic because the exact CI could not be computed.

5.2 Pharmacokinetic properties

The absorption characteristics of [MA177 trade name] have been determined after administration of tablets of [MA177 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** arithmetic mean ± SD	
	Dihydroartemisinin	**Piperaquine**
Maximum concentration (C_{max}) ng/mL	266 ± 133	123 ± 85[#]
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.hour/mL	542 ± 229	2029 ± 926*
Time to attain maximum concentration (t_{max}) hour	1.37 ± 0.77	3.49 ± 1.36

* $AUC_{0\text{-}72h}$ (µg.h/mL) # C_{max} (µg/ml)

	Dihydroartemisinin	Piperaquine
General		
	Bioavailability is higher in patients with malaria compared to healthy volunteers.	
Absorption		
Absolute bioavailability	NA	NA
Oral Bioavailability	NA	NA
Food effect	Exposure increased by 43% with a high fat/high calorie meal	Exposure increased approximately 3-fold with a high fat/high calorie meal
Distribution		
Volume of distribution (mean)	0.8 L/kg	730 L/kg
Plasma protein binding *in vitro*	44–93%	> 99%
Tissue distribution	Accumulates in red blood cells	Accumulates in red blood cells
Metabolism		
	Hepatic glucuronidation to α-artenimol-β-glucuronide	Hepatic: major metabolites are a carboxyl acid cleavage product and a mono-N-oxidated product
Elimination		
Mean elimination half-life	1 hour	22 days
Mean oral clearance	1.34 L/h/kg	2.1 L/h/kg
% of dose excreted in urine	Negligible as intact drug	NA
% of dose excreted in faeces	Negligible as intact drug	NA
Pharmacokinetic linearity	NA	NA
Drug interactions *(in vitro)*		
Transporters	NA	NA
Metabolising enzymes	UGT1A9 and UGT2B7	CYP3A4 (mainly), CYP2C9 and CYP2C19
	Inhibitor of CYP1A2	Mild inhibitor of CYP3A4 and CYP2C19 Inducer of CYP2E1
Special populations		
Renal impairment	NA	NA
Hepatic impairment	NA	NA
Elderly patients	NA	NA

NA: Not available

Patients with hepatic or renal insufficiency

No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or in elderly people.

Paediatrics

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for dihydroartemisinin pharmacokinetics between the paediatric and adult populations. The mean clearance (1.45 L/h/kg) was slightly faster in the paediatric patients than in the adult patients (1.34 L/h/kg), while the mean volume of distribution in the paediatric patients (0.705 L/kg) was lower than in the adults (0.801 L/kg).

The same comparison showed that piperaquine absorption rate constant and terminal half-life in children were predominantly similar to those seen in adults. However, the apparent clearance was faster (1.30 versus 1.14 L/h/kg) and the apparent total volume of distribution was lower in the paediatric population (623 versus 730 L/kg).

5.3 Preclinical safety data

General toxicity

Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts.

The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible.

Dihydroartemisinin and piperaquine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

No carcinogenicity studies have been performed.

Dihydroartemisinin causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally, the development, behaviour and growth of the surviving progeny was normal following exposure *in utero* or via milk.

No reproduction toxicity studies have been performed with the combination of dihydroartemisinin and piperaquine.

Central nervous system (CNS) toxicity

There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different dihydroartemisinin pro-drugs. In humans, the potential neurotoxicity of orally administered dihydroartemisinin can be considered highly unlikely, given the rapid clearance of dihydroartemisinin, and its short exposure (3 days of treatment for malaria patients). There was no evidence of dihydroartemisinin-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity

Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC50 was 0.15 μmol for piperaquine and 7.7 μmol for dihydroartemisinin. The association of dihydroartemisinin and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns with dihydroartemisinin, as it does not absorb in the range of 290–700 nm. Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: maize starch
dextrin
hypromellose
sodium starch glycolate
magnesium stearate

Film coat: polyvinyl ethanol
titanium dioxide
talc
macrogol/polyethylene glycol
FD&C Blue #2/indigo carmine aluminium lake
lecithin (soya)
FD&C blue #1/brilliant blue FCF aluminium lake
FD&C yellow #6/sunset yellow FCF aluminium lake

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25℃. Store in the original pack in a place protected from light and humidity.

6.5 Nature and contents of container

Plastic (PVC) on aluminium foil blister cards.

Plastic (PVC) on aluminium foil blister cards. The blister cards are sealed in a plastic (PET/PE) and aluminium pouch inside the carton.

Aluminum-PVC blister of 6 tablets; 2 blisters / outer pouch bag; 1 pouch /carton.
Pack size: 2 x 6 x 1 tablets.

Aluminum-PVC blister of 6 tablets; 1 blister / outer pouch bag; 1 pouch /carton.
Pack size: 1 x 6 x 1 tablets.

Aluminum-PVC blister of 6 tablets; 1 blister / outer pouch bag; 25 pouch /carton.
Pack size: 1 x 6 x 25 tablets.

Aluminum-PVC blister of 9 tablets; 1 blister / outer pouch bag; 1 pouch /carton.
Pack size: 1 x 9 x 1 tablets.

Aluminum-PVC blister of 9 tablets; 1 blister / outer pouch bag; 25 pouch /carton.
Pack size: 1 x 9 x 25 tablets.

Aluminum-PVC blister of 3 tablets; 1 blister / outer pouch bag; 25 pouch /carton.

Pack size: 1 x 3 x 25 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
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)

MA177

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

November 2025

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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