Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Artemether

Proprietary Product Name: ArTiMist 6

Sponsor: Suda Pharmaceuticals Ltd

December 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACT	Artemisinin based combination therapy
AE	Adverse event
ART	Artemether
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve from time zero up to time t
$AUC_{0-\infty}$	Area under the plasma concentration-time curve to infinity
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CYP	Cytochrome P450
DHA	Dihydroartemisinin
FAS	Full analysis set
FASII	Bacterial type II fatty acid synthesis
FCT	Fever clearance time
GI	Gastrointestinal
h	Hour(s)
IM	Intramuscular
IV	Intravenous
L	Litre(s)
LBS	Literature based submission
L/h	Litre(s) per hour
mg	Milligram(s)
MITT	Modified intention to treat
ng	Nanogram(s)

Abbreviation	Meaning
PCR	Polymerase chain reaction
PCT_{50}	Time for parasite count to fall by 50%
PCT_{90}	Time for parasite count to fall by 90%
PD	Pharmacodynamic(s)
PfK13	*P. falciparum* Kelch13
PI3K	Phosphoinositide 3-kinase
PI3P	Phosphatidylinositol 3-phosphate
PK	Pharmacokinetic(s)
PP	Per protocol
PRR_{24}	Parasite reduction ratio at 24 hours
SAE	Serious adverse event
SL	Sublingual
TEAE	Treatment-emergent adverse event
T1, T2, T3, T4	Treatment groups 1 to4 in Study ART001
T_{max}	Time to reach maximum plasma concentration
UPR	Unfolded protein response
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Rejected
Date of decision:	14 May 2019
AAT outcome*	Appeal was withdrawn[1]
Date of entry onto ARTG:	Not applicable
ARTG number:	Not applicable
▼ *Black Triangle Scheme*	Not applicable
Active ingredient:	Artemether
Product name:	ArTiMist 6
Sponsor's name and address:	SUDA Pharmaceuticals Ltd Level 1, Unit 12, 55 Howe St Osborne Park WA 6017
Dose form:	Spray solution
Strength:	6.17 mg
Container:	Pump actuated metered dose spray unit
Pack size:	One
Approved therapeutic use:	Not applicable
Route of administration:	Sublingual
Dosage:	Proposed *Children and infants weighing 5 kg to 15 kg* ArTiMist 6 should be administered sublingually at a dose of 3 mg/kg starting at the time of initial diagnosis and again after 8 hours, 24 hours, 36 hours, 48 hours, and at 60 hours and every 24 hours until the patient returns to normal *per os*.

*AAT= Administrative Appeals Tribunal

[1] The sponsor appealed to the AAT for a review of the TGA's decision not to register Artemether.

Product background

This AusPAR describes the application by SUDA Pharmaceuticals Ltd (the sponsor) to register ArTiMist 6 (artemether) spray solution for the following proposed indication:

- *For the initial treatment of children with severe falciparum malaria weighing between 5 and 15 kg*
- *For the initial treatment of children with falciparum malaria who cannot take (or reliably take) oral medication due to gastrointestinal complications such as vomiting or diarrhoea.*

Malaria infection is caused by the *Plasmodium* species of parasite which is transmitted via the bite of the female *Anopheles* mosquito. The disease is endemic throughout the tropical with approximately 3.2 billion people living in malaria-endemic countries. The World Health Organization (WHO) estimates that there were some 214 million cases of symptomatic malaria in 2015.[2] The estimated number of deaths was 438,000. Most cases and deaths (88%) occur in the African region and the largest burden of malaria disease is caused by *Plasmodium falciparum*.

Following the bite of a malaria-infected mosquito, the inoculated sporozoites travel to the liver within one to two hours. Symptoms become apparent during the erthrocytic stage of the parasite life cycle. The release of the merozoites from infected red blood cells, via cell rupture, causes fever and other manifestations. Severe malaria is the result of the red blood cells adhering to the small blood vessels causing infarcts, capillary leakage and organ dysfunction. This can result in altered consciousness, seizures, respiratory distress and pulmonary oedema, circulatory collapse, metabolic acidosis, renal failure, haemoglobinuria, coagulopathy and disseminated intravascular coagulation, anaemia and hypoglycaemia. Severe malaria is a medical emergency and death is highly likely if untreated. The mortality risk increases if the patient cannot take oral medications reliably, has a high parasite count or has evidence of vital organ dysfunction. However, with effective treatment and supportive care mortality rates fall to 10 to 20%. Therefore, for the treatment of severe malaria, it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible.[3]

Artemether is a semi-synthetic drug substance synthesised in a two-step process from the starting material, artemisinin, which is derived from the leaves of the sweet wormwood (*Artemisia annua)* plant. Artemether is an antimalarial agent. Artemisinins act against ring stages, early and late trophozoites, and schizonts malaria parasites. Artemisinins are only active against blood stages of the parasite and are not active against liver or mosquito stages. Artemether and the artemesinin class in general are considered to be highly effective and well tolerated with a wide therapeutic index.[3] Artemisinin-based combination therapies (ACT) are also the treatment of choice for uncomplicated malaria. Treatment with ACT is recommended in order to reduce treatment duration and to prevent the emergence of drug resistance. Oral artemesinin-based monotherapy is not recommended by the WHO due to this risk of drug resistance.

Given risk of death in young children with severe malaria, prompt effective treatment is imperative. In malaria-endemic regions appropriate medical facilities may not be nearby, therefore treatment should be initiated prior to transport to the facility. Minimising any delay in treatment commencement may have a positive impact on malaria mortality.

Oral artemether has low and variable bioavailability and is not feasible if the child is unable to take oral therapy. Intravenous or intramuscular administration requires skill on

[2] World Health Organization (2016). *WHO World Malaria Report 2015*. WHO, Geneva 2016
[3] World Health Organization (2015). *Guidelines for the treatment of malaria.* Third edition. Geneva, Switzerland: WHO Press.

the part of the person administering the therapy. Rectal suppositories also may not be reliable if the gastrointestinal tract is not functioning adequately. The clinical rationale for the sublingual product is to have an effective medication that can be easily and promptly given so that clinical stability can be achieved and oral administration of full treatment with an ACT can then be given.

Regulatory status

ArTiMist 6 (artemether) is a sublingual spray proposed for the initial treatment of severe falciparum malaria. Combination products containing artemether that have previously been approved in Australia (all sponsored by Novartis Pharmaceuticals Australia Pty Ltd) and are registered on the Australian Register of Therapeutic Goods (ARTG) are as follows:

- AUST R 90011 Riamet (artemether/lumefantrine) 20 mg/120 mg tablet blister pack. Registered 24 July 2002.
- AUST R 158523 Riamet 20 mg/120 mg (artemether/lumefantrine) 20 mg/120 mg dispersible tablet blister pack. Registered 9 July 2010.
- AUST R 158527 Coartem 20 mg/120 mg (artemether/lumefantrine) dispersible tablet blister pack. Registered 9 July 2010.

The sponsor is not intending to market this proposed product in Australia. The sponsor states they have selected the TGA as a stringent regulatory authority for prequalification. Their medicine is intended for the treatment of malaria in malaria endemic countries (for example , Ghana, Ethiopia and Kenya). The sponsor would like ArTiMist to be adopted on to the World Health Organization (WHO) Guidelines for the Treatment of Malaria.

At the time the TGA considered this application no similar applications have been approved or are planned in any other countries except Australia.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2016-04637-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2017
First round evaluation completed	5 October 2017
Sponsor provides responses on questions raised in first round evaluation	13 December 2018
Second round evaluation completed	28 February 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 March 2019

Description	Date
Sponsor's pre-Advisory Committee response	19 March 2019
Advisory Committee meeting	4 April 2019
Registration decision (Outcome)	14 May 2019
Number of working days from submission dossier acceptance to registration decision*	177

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate of the Secretary's (herein referred to as the 'Delegate') overview and recommendations.

Quality

Quality aspects of the product are acceptable. The dose form is manufactured in Canada.

The evaluation has drawn attention to 3 matters.

Artemether and Artemether Spray Solution are not subject to British Pharmacopoeia, United States Pharmacopeia or European Pharmacopoeia monographs. Each metered dose contains 6.17 mg artemether. For a 15 kg patient a total of 7 actuations per dose are required. The maximum recommended daily dose of artemether is 90 mg for a child weighing between 13.5 to 15 kg. ArTiMist 6 should not be used for more than 7 days. The pack is labelled as 50 actuations although it contains enough liquid to give approximately 60 actuations before the volume in each activation starts to fall off.

The lack of absolute bioavailability study and lack of a food effect study are drawn to the attention of the Delegate. The sponsor has justified the lack of an absolute bioavailability study on the basis that no intravenous (IV) formulation for artemether (a highly lipid soluble drug) is currently available for either human or toxicological use. The sponsor has justified the absence of a food effect study on the basis that patients are advised that they should not eat or drink 10 minutes before and after administration of ArTiMist and ArTiMist is contraindicated in patients who can take food.

Nonclinical

The nonclinical submission was entirely literature based. No primary or secondary pharmacology studies were conducted with the formulation. Due to the extensive clinical experience using artemisinin derivatives to treat malaria, this is acceptable.

Resistance to artemisinin-based therapy was not addressed in the nonclinical submission. *P. falciparum* has been shown to develop resistance to artemisinin monotherapy over time Artemisinin resistance is associated with increased unfolded protein response (UPR), dysregulation of the pre-replication phase and the phosphoinositide 3-kinase (PI3K)/phosphatidylinositol 3-phosphate (PI3P)/Akt pathway. A mutation of the *P. falciparum* Kelch13 (PfK13) propeller domain endows the parasites with an increased

ability to enter the quiescent state. PfK13-mutant (resistant) parasites have greater UPR expression and mobilisation, which increase their capacity to manage oxidative damage and to repair or degrade proteins damaged by alkylation and oxidation generated by artemisinin. These parasites also have an elevated production of PI3P, which could play a role in the maintenance of a minimal energetic metabolism based on mitochondrial and apicoplast activity. The quiescence state is maintained by alternative tricarboxylic acid cycle and bacterial type II fatty acid synthesis (FASII) metabolism, until drug removal/excretion when parasites can resume growth. The WHO does not recommend artemisinins are used as monotherapy in the treatment of malaria due to the risk of potentiating treatment resistance.[3] Given the risk of potentiating treatment resistance, the nonclinical evaluation considers it would be advisable to use ArTiMist only when parenteral therapy is not available.

The main toxicity of clinical concern with artemether is the potential for neurotoxicity. Since very young animals seem to be more sensitive to neurotoxicity than adult animals, and the toxicity of sublingual ArTiMist has not been assessed in animals of any age, the nonclinical evaluation recommends that the treatment of children weighing 5 to 15 kg with ArTiMist is limited to less than 4 days. However, a longer treatment duration can be acceptable if supported by clinical data.

There are no nonclinical objections to registration provided local effects at the site of administration have been adequately addressed by clinical data.

Clinical

The clinical dossier contained four clinical trials:

- Study ART001: a single dose pharmacokinetic (PK) study in adults;
- Study ART002: a multi-dose PK study in adults;
- Study ART003: an exploratory Phase IIa efficacy and safety study; and
- Study ART004: a Phase III efficacy and safety study.

It also contained a large number of literature references.

Pharmacokinetics

Two clinical PK studies were submitted:

- Study ART001 a single dose PK study in adults; and
- Study ART002 a multi dose PK study in adults.

PK was also assessed in the target population in Studies ART003 and ART004.

Study ART001 assessed the relative bioavailability of sublingual (SL) sprays 3 mg/actuation and 6 mg/actuations (2 strengths) and 15 mg and 30 mg doses with a single oral dose of 30 mg artemether in 16 healthy adult males. The treatment groups were as follows:

- Treatment 1 (T1): 15mg SL dose by 3 mg/actuation;
- Treatment 2 (T2): 30mg SL dose by 3 mg/actuation;
- Treatment 3 (T3): 30mg SL dose by 6 mg/actuation; and
- Treatment 4 (T4); 30 mg oral tablet.

PK parameters were measured for artemether and the more biologically active metabolite dihydroartemisinin (DHA). The time to reach maximum plasma concentration (T_{max}) was

around 1.7 hours. The ratio of mean log area under the plasma concentration-time curve from time zero up to 12 hours (AUC_{0-12}) was 229% and 213% for T2/T4 and T3/T4, respectively. For DHA, the ratio of mean log AUC_{0-12} was 264% and 239% for T2/T4 and T3/T4, respectively. The relative bioavailability, as measured by AUC_{0-12}, $AUC_{0-\infty}$, and maximum plasma concentration (C_{max}) of artemether in Study ART001, of the 3 mg/actuation and the 6 mg/actuation formulations was similar. This was also the case for the AUC_{0-12} and C_{max} of DHA. The C_{max} of artemether and DHA was dose proportional between the 15 (T1) and 30 mg (T2) SL sprays. AUC_{0-12} was less than dose proportional for both artemether (25.8 versus 76.6 ng.h/mL) and DHA (29.6 versus 99.5 ng.h/mL). This is likely due to the shorter elimination half-life ($t_{1/2}$) of the 15 mg dose.

Study ART002 assessed the bioequivalence of 30mg SL spray given by 3 mg and 6 mg/actuation for 5 days in 16 healthy African males. For artemether $AUC_{0-\infty}$ the ratio of means (Day 5 to Day 1) was 0.96 (90% confidence interval (CI): 0.19, 1.080.60, 1.32) and 1.3 (90% CI: 0.19, 1.080.36, 2.25) for the respective formulations. After 5 days dosing the C_{max} and AUC_{0-last} for DHA increased (30 to 59% for C_{max} and 62 to 70% for AUC_{0-last}), indicating accumulation of DHA. There were no major differences in the PK parameters of the two formulations of 6 mg and 3 mg per actuation. Bioequivalence was not demonstrated on all parameters although the Phase I studies were not powered to assess this formally.

Pharmacokinetics in the target population was assessed by non-compartmental PK analyses in efficacy Studies ART003 and ART004. In Study ART003, plasma levels close to the target of 200 ng/mL were reached at 45 minutes post first dose and the C_{max} of 271 ng/L was achieved at 1.6 hours. For DHA, a C_{max} of 107 ng/mL was reached by 2 hours. There was high variability in artemether and DHA concentrations. In Study ART004, at 45 minutes post the first dose the mean artemether plasma concentration was 211.2 ng/mL and a C_{max} of 333.2 ng/mL was reached at 1.3 hours. After the third dose the mean C_{max} of 224.4 ng/mL was reached at 2.3 hours post dose. On Day 2, after 3 doses, the DHA C_{max} of 315.4 ng/mL was measured at 2.8 hours post dose.

In the paediatric patients, target artemether levels (200 ng/mL) were reached by 45 minutes post first dose and the C_{max} was achieved at around one a half hours. DHA showed evidence of accumulation in children and by Day 2 a 5 fold increase in C_{max} and 10 fold increase in $AUC_{0-\infty}$ was found.

A population PK analysis was undertaken on the healthy subjects (Studies ART001 and ART002) and the paediatric patients (Studies ART003 and ART004) and the models were the subject of two literature reports.[4,5] Studies ART003 and ART004 included 824 plasma concentrations for artemether and 788 concentrations for DHA. It was proposed that there is more SL absorption in healthy adults than sick young children due to longer SL retention time. In addition, in children, some artemether is swallowed and absorbed via the gastrointestinal (GI) tract.

Artemether is rapidly metabolised by the liver to DHA mainly via cytochrome P450 (CYP) 3A4/3A5 and to a lesser extent CYP2B6. DHA is then metabolised to largely inactive compounds. As hepatic metabolism is the main clearance mechanism, caution will be required in patients with severe hepatic impairment. As artemether is metabolised by CYP3A4 and inducers of CYP3A4 may reduce artemether levels, therefore strong CYP3A4 inducers are contraindicated.

[4] Salman, S. et al (2015 a). Pharmacokinetics of a novel sublingual spray formulation of the antimalarial drug artemether in healthy adults. *Antimicrob Agents Chemoth*. 2015; 59, 3197-3207.
[5] Salman, S. et al (2015 b). Pharmacokinetics of a novel sublingual spray formulation of the antimalarial drug artemether in African children with malaria. *Antimicrob Agents Chemother*. 2015; 59: 3208–3215.

TGA replication of the population PK analysis suggested there are no barriers to registration arising from the evaluations of the population PK.

Pharmacodynamics

No pharmacodynamics (PD) studies were submitted. The primary PD effect of artemether is parasite clearance. In the paediatric patient Studies ART003 and ART004, the mean parasite clearance times were 35.7 hours and 30.3 hours, respectively. In the literature, most studies have failed to demonstrate a correlation between parasite clearance time and drug concentration.

Resistance to artemisinin-based therapy has not been assessed by the sponsor. Artemisinin resistance has been reported in parts of South East Asia. The Worldwide Antimalarial Resistance Network states that a major focus for containing resistance is the cessation of artemisinin-based monotherapy.

Dose selection for efficacy studies

The sponsor's response to TGA questions from the first round clinical evaluation report has described that a dose of 3 mg/kg in patients was expected to give an artemether C_{max} and AUC of between 200 to 400 ng/mL and 400 to 800 ng.h/mL, respectively, which is known to be in the therapeutic and safe range. The comparable exposure to artemether and DHA in paediatric and adult patients with malaria was based literature and on data from the PI for Riamet (artemether/lumefantrine) combination product.

Efficacy

Two studies in the dossier which provided efficacy data: Studies ART003 and ART004. Study ART003 was a Phase IIa study and Study ART004 the pivotal efficacy study.

Study ART004

Study ART004 was a Phase III, randomised, open label, active controlled, multicentre, superiority trial of ArTiMist versus IV quinine in 151 children with severe or complicated falciparum malaria, or children with uncomplicated malaria with GI complications. It was conducted at 3 sites (Rwanda, Ghana and Burkina Faso) between November 2010 and September 2012. The study is presented in the clinical evaluation report.

The primary objective was to demonstrate the superiority of ArTiMist over IV quinine in establishing parasitological success (reduction of parasite counts by ≥ 90% within 24 hours).

Inclusion criteria were: children weighing between 5.00 kg and 15.00 kg inclusive; falciparum malaria as evidenced by thick or thin blood smears of ≥ 500 *P. falciparum* per µL (patients with mixed infections could be included provided ≥ 500 *P. falciparum* per µL); either severe or complicated falciparum malaria as determined by the investigator based on WHO criteria for severity, and/or uncomplicated falciparum malaria unable to tolerate oral medication as a result of GI complications such as vomiting or diarrhoea.

ArTiMist was given sublingually at a dose of 3 mg/kg. In the first 3 days, 6 doses in total were given at 0, 8, 24, 36, 48 and 60 hours. This was followed by a further 4 days of ArTiMist or oral therapy according to local guidelines. The formulation of artemether was 6 mg per actuation.

IV quinine (600 mg/2 mL) was given as per local guidelines with an initial loading dose of 20 mg/kg over 4 hours and then 10 mg/kg every 8 hours. Once able to swallow, treatment

was changed to quinine syrup, crushed tablets or combination therapy so that treatment continued for at least 7 days.

If there was inadequate response at 24 hours, rescue medication could be given.

The study included a 4 day inpatient period, and then follow up visits on Days 7, 14, 21 and 28.

The primary efficacy variable was blood parasite counts (thick and thin smears). These were assessed at the local site and also sent to a central laboratory for blinded assessment. Only the data from the central laboratory was used for efficacy analysis. Other variables were parasite polymerase chain reaction (PCR) genotyping, temperature, level of consciousness and *per os* (oral administration) status.

The primary efficacy endpoint was parasitological success defined as a reduction in parasite count ≥ 90% of Baseline at 24 hours after the first dose. Secondary efficacy objectives included complete cure, parasite clearance, fever clearance time (FCT), early and late treatment failures, late parasitological failures and time to normal clinical status.

Subject disposition; there were 180 subjects screened and 151 randomised with 77 and 74 in the ArTiMist and quinine groups, respectively. The completion rate was the same in the two groups (97%). The modified intention to treat (MITT) population included 70 and 71 subjects, respectively (93.4%). The per protocol (PP) population included 137 subjects (90.7%).

Demographic and baseline characteristics were similar between groups. The mean age was 2.8 and 2.5 years in the artemether and quinine groups, respectively. All subjects were black African. Subjects were more likely to have severe or complicated malaria (63.6% to 68.9%) than uncomplicated malaria with GI complications (31.1% to 36.4%). The mean weight was 11 kg. The mean parasite count pre-dose on Day 1 was 87,498 and 72,284 *P. falciparum*/µL in the artemther and quinine groups, respectively. The rate of Blantyre Coma Scale < 5 at Baseline was 22.1% and 28.4%, respectively.[6] All children (except for one) with uncomplicated malaria with GI complications were at site [Information redacted].

Subjects finished their antimalarial therapy with artesunate-amodiaquine (9.1% and 9.5% in the artemether and quinine groups, respectively) or artemether-lumefantrine (61.0% and 82.4% in the artemether and quinine groups, respectively). The lower rate in the artemether group was due to one site finishing the 7 days of therapy with ArTiMist.

Results for the primary efficacy outcome; rate of parasitological success (reduction of parasite counts by ≥ 90% within 24 hours) in the MITT population was 94.3% in the ArTiMist group and 39.4% in the IV quinine group. The difference of 54.8% (95% CI: 42.3, 67.5) was significant ($p < 0.005$) thus superiority was achieved. In the PP analysis (parasitological success rates of 95.6% versus 40.6%). Study site was a significant factor in the model and when adjusting for this factor the difference in success rates between ArTiMist and quinine was 30.4% (95% CI: 9.4, 98.7) in the MITT population.

Results for other efficacy outcomes; parasite clearance (two successive negative smears) was similar between groups (100% versus 94.4%), however the mean parasite clearance time was faster with ArTiMist (30.3 versus 68.0 hours, $p < 0.005$). The faster clearance was also demonstrated on the mean time for parasite count to fall by 50% (PCT_{50}; 9.4 versus 18.6 hours) and time for parasite count to fall by 90% (PCT_{90}; 15.0 versus 27.9 hours). The mean percentage parasite reduction ratio at 24 hours (PRR_{24}) was 98.2% versus 44.5% ($p < 0.005$). There were no early treatment failures in the ArTiMist group

[6] The Blantyre Coma Scale is a modification of the Paediatric Glasgow Coma Scale designed for use in assessing children with malaria, with a composite minimum and maximum score of 0 and 5 respectively. All scores < 5 are considered abnormal.

and 10 (14%) in the quinine group with one of these subjects needing rescue therapy. The late parasitological failure rate was similar between group (17.1% versus 19.7% p = 0.95).

Of the subjects with available data (55 out of 70 and 63 out of 71 in the artemether and quinine groups, respectively), the complete cure rate was 74.5% and 73.0%, respectively, with no significant difference between groups (p = 0.99). The late clinical failure rate was 4.3% versus 1.4%. The fever clearance time, time to return to normal *per os*, and time to return to normal level of consciousness were similar between groups.

The clinical evaluation report comments that the study was not designed primarily to assess clinical endpoints. There was also no controlling for multiplicity in the analysis of a large number of secondary endpoints. As such, the data on secondary endpoints only provide limited support for efficacy.

Study ART003

Study ART003 was an open label, randomised, controlled study conducted at one hospital site in Rwanda in 2009 to 2010. The primary objective was to compare the efficacy of ArTiMist 3 mg/kg to IV quinine in reducing the parasite count by 90% within 24 hours in children with severe or complicated falciparum malaria, or children with uncomplicated malaria with GI complications.

Subjects were randomised to ArTiMist 3 mg/kg or IV quinine in a 1:1 ratio. Both formulations of 3 mg/actuation and 6 mg/actuation were used. Quinine 20 mg/kg was given as a loading dose over 4 hours followed by 10 mg/kg 8 hourly and oral Coartem (artemether/lumefantrine combination product) once oral dosing was possible.

The study included children weighing 5 to 15 kg with severe or complicated malaria or uncomplicated malaria but unable to tolerated oral medication due to gastrointestinal complications. Falciparum count of > 500 per µL on thick or thin blood smear was required.

The primary efficacy variable was parasite count with the primary endpoint of parasitological success being defined as a reduction in parasite count of ≥ 90% from Baseline at 24 hours after the first dose. Efficacy was analysed on the full analysis set (FAS); this included all patients who received at least one dose of medication and had at least one parasite count at 12 or 24 hours post the first dose of study medication.

16 children were screened and enrolled in the ArTiMist group and 15 in the quinine group. One subject was withdrawn due to a protocol violation. Mean age was 3.0 to 3.6 years with a mean weight of 11 kg. Most children had severe or complicated malaria (62.5% and 80.0% in the ArTiMist and quinine groups, respectively). Baseline median parasite counts were 19,660 and 21,800 parasites/mL, respectively.

The rate of parasitological success was 93.3% and 66.7% in the ArTiMist and quinine groups, respectively. The difference of 26.7% (95% CI: -0.3%, 53.7%). At 24 hours, the proportion of patients with negative smears was 73.3% and 40% for ArTiMist and quinine groups, respectively. There was also no significant difference in the mean time to PCT_{90} or PCT_{50}.

Safety

There were 125 subjects exposed to ArTiMist in the clinical development program, 32 were healthy adults and 93 were children (5 to 15 kg) with severe or complicated falciparum malaria or with uncomplicated falciparum malaria who could not take oral medication.

In Study ART004 the treatment-emergent adverse event (TEAE) rate was 55.8% and 59.5% in the ArTiMist and quinine groups, respectively. The most frequent TEAEs (ArTiMist versus IV quinine) were anaemia, (7.8% versus 16.2%), pyrexia (9.1% versus

8.1%), vomiting (6.5% versus 2.7%), respiratory tract infection (9.1% versus 4.1%), proteinuria (1.3% versus 5.4%), cough (7.8% versus 2.7%) and bronchitis (5.2% versus 2.7%).

There were no TEAEs related to local oral tolerability of the SL product in any subject during the clinical development program.

The percentage of subjects with a treatment-related TEAE in Study ART004 was 6.5% and 8.1% in the ArTiMist and quinine groups, respectively. The treatment-related TEAEs in the ArTiMist group (5 subjects) were diarrhoea (2 cases), vomiting (2 cases), parotitis and cough.

The serious adverse event (SAE) rate in Study ART004 was 6.5% (n = 4) and 8.1% (n = 10) in the ArTiMist and quinine groups, respectively. In the ArTiMist group, the SAEs were anaemia (n = 2), bronchopneumonia and sepsis.

There were no subjects who discontinued SL artemether due to an adverse event (AE), while there were 2 in the quinine group.

In Study ART003 the TEAE rate was 81.3% and 73.3% in the ArTiMist and quinine groups, respectively. The most frequent TEAEs were pyrexia (37.5% versus 33.3%), malaria (12.5% versus 26.7%) and upper respiratory tract infection (31.3% versus 6.7%).

There were no treatment-related TEAEs in Study ART003 or in the healthy volunteer studies.

There was 1 SAE in the quinine group in Study ART003.

There were no deaths in the clinical development program.

The risk of neurotoxicity with chronic dosing in animals does not appear to be evident in humans.

In Study ART004, the rate of subjects with clinically significant abnormal biochemistry was highest on Day 0 (16.9% versus 9.5%) and by Day 21 all abnormalities had resolved. Overall, 12 of the 13 cases in the ArTiMist group had elevated direct and/or total bilirubin. In Study ART003 there were no cases of clinically significant biochemistry results. Renal findings were unremarkable in Study ART004.

In Study ART004 the rate of clinically significant haematology results was 20.8% and 16.2% on Day 0 in the ArTiMist and quinine groups, respectively. These had resolved by Day 21.

There were two ArTiMist and seven quinine treated subjects with an SAE of anaemia.

In Study ART003, the rate of clinically significant abnormal haematology at study entry was 18.8% and 26.7%, respectively. All cases were normal by Day 21.

The clinical evaluation report concludes that in line with this large amount of literature on artemether use in children and adults, in this limited clinical safety dataset SL artemether was well tolerated by the young children. The risk of neurotoxicity with chronic dosing in animals does not appear to be evident in humans.

Benefit-risk assessment

The clinical evaluation report has identified benefits as:

- ArTiMist was effective at clearing *P. falciparum* parasites in children with severe malaria;
- on clinical endpoints, the efficacy of ArTiMist was in line with IV quinine;
- artemether is an effective and widely used medication in adults and children;

- the SL formulation was well tolerated;
- the SL formulation has demonstrated rapid absorption and higher bioavailability than oral tablets;
- the SL formulation would be easy to administer with possibility it could be given prior to transfer to a hospital; and
- the potential for a significant public health benefit.

The clinical evaluation report has identified risks as:

- the ArTiMist clinical trial database is very small, although there is extensive literature on other formulations of artemether;
- safety risks of haemotoxicity, cardiotoxicity, hypersensitivity, audio-neural toxicity and reproductive toxicity, although there is extensive literature safety data that indicate the level of these risks is low;
- possible drug interactions;
- lack of comparative data with the current recommended treatment for severe falciparum malaria in children; and
- the WHO does not recommend artemisinins are used as monotherapy in the treatment of malaria due to the risk of potentiating treatment resistance.

The evaluator finds that SL artemether demonstrated efficacy and safety in the small clinical trial program and this was supported by a very large database of literature which is in favour of the product's use. In addition, given it may be used easily prior to transfer to hospital, ArTiMist has a clear clinical place as a second line therapy in initial treatment of severe falciparum malaria when parenteral artesunate is not available. For the sub-indication of treatment of children with uncomplicated falciparum malaria who cannot take oral medications, the evaluator concludes that the benefit risk profile is positive.

Risk management plan

The TGA granted a waiver for submission of a risk management plan (RMP) on the basis that the product was not intended for marketing in Australia. The sponsor stated that prior to commercialisation of ArTiMist, the sponsorship of ArTiMist will be transferred to a nominated party who will be responsible for post-marketing activities.

Risk-benefit analysis

Delegate's considerations

The quality evaluation report has drawn attention to the number of actuations required for treatment of child of 13.5 to 15 kg. The Delegate notes target concentrations of artemether and DHA were achieved in clinical studies with this dosage. The Delegate accepts the sponsor's justification for lack of an absolute bioavailability and lack of a food effect study.

The nonclinical evaluation report recommended that duration of treatment with ArTiMist be limited to 4 days. The clinical studies included treatment for up to 7 day and with good local tolerability.

At the time the clinical studies (2009 to 2010) were commenced, IV quinine was considered by the WHO as the first line of treatment for children with severe or

complicated falciparum malaria with GI complication. The TGA have provided confirmation that they are also of the opinion that IV quinine is an acceptable comparator as it is registered and recommended as an alternative treatment for severe *P falciparum* malaria in Therapeutic Guidelines.[7] During the conduct of Study ART004, the WHO changed their treatment recommendations for severe childhood malaria to state that IV or intramuscular (IM) artesunate (2.4 mg/kg body weight) is the treatment of choice and that only if parenteral artesunate is not available should artemether IM or quinine (IV or IM) be given.[3] This should be followed by a full dose of effective artemisinin-based combination therapy (ACT) orally. The proposed indications for ArTiMist 6 have been amended during the evaluation process to state:

> *[...] in severe falciparum malaria ArTiMist 6 should only be used when therapy with parenteral artesunate is not available.*

The clinical rationale initially given for the SL product is to have an effective medication that can be easily and promptly given to young children with severe malaria so that clinical stability can be achieved. The sponsor has subsequently proposed that ArTiMist could be used as a frontline treatment for severe malaria outside the hospital setting. The clinical evaluation report considers that this SL treatment could be given by non-medical personnel. The clinical evaluation report recommends that a post-marketing surveillance study is carried out to assess treatment efficacy in this field setting. The sponsor has also committed to development of an education program for health care providers to ensure the product remains within the health care system and does not reach the public domain.

The first round clinical evaluation report recommended conduct of a clinical trial comparing the efficacy of SL artemether to parenteral artesunate in children with severe falciparum malaria. The sponsor has stated that conduct of such a clinical study would be unethical. The risk/benefit for parenteral artesunate is exceptionally favourable where there is access to this treatment.

This Category 1 application is a 'mixed' application (literature based submission (LBS) and clinical studies) to address the nonclinical and clinical aspects of the application. The search strategy for the LBS was approved by the TGA on 4 May 2016.

The clinical study program has been limited to treatment of 93 young children and only 125 subjects in total have been exposed to SL artemether.

Efficacy was reported in one pivotal clinical study based on clearance of *P. falciparum* parasites in children with severe malaria or unable to take oral medication. The study was not designed for primary assessment of clinical outcomes.

A significant risk with ArTiMist 6 is the resistance risk with the monotherapy. Numbers of statements in the Product Information (PI) and Consumer Medicines Information (CMI) have been included to mitigate this risk. The sponsor provides a commitment to develop an education program for health care providers (which would include educational material/medication guides) prior to commercialisation of the product in malaria endemic countries. The aim of the program will be to ensure the product remains within the health care system and does not reach the public domain.

The sponsor provides a commitment to work collaboratively with the WHO and to ensure adequate measures are in place to minimise the potential risk to treatment resistance with the monotherapy prior to launch.

No RMP was submitted as agreed at the outset of the submission application. Potential for misuse of the monotherapy in malaria endemic countries cannot be assessed. The 6 mg dose per actuation strength does restrict potential for misuse in older children and adults.

[7] Therapeutic Guidelines: Antibiotic, Version 15, 2014, Therapeutic Guidelines Limited, Melbourne.

Proposed action

The Delegate was not in a position to say, at this time, that the application for ArTiMist 6 should be approved for registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACM consider there is a potential role for this sublingual monotherapy product for initial treatment of severe falciparum malaria in young children in endemic countries, given ArTiMist 6 should only be used when therapy with parenteral artesunate is not available? The clinical evaluation report considers that this sublingual treatment could be given by non-medical personnel. The sponsor has committed to an educational program to ensure the product remains within the health care system and does not reach the public domain.
2. Has efficacy for the new product been adequately established in the one small pivotal clinical study?
3. Has the safety of the product for the new product been adequately established given clinical study program has involved only 93 children?
4. Has the risk of potentiation of resistance associated with this monotherapy product been adequately addressed by changes to draft PI and CMI, and the sponsor's commitments to provide an educational program for health care providers and to work with the WHO to minimise this risk?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[8]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the Delegate in relation to the application to register ArTiMist 6, in the form of 6 mg per actuation sublingual spray (60 mg/mL solution of artemether).

The ACM agreed that ArTiMist 6 had an overall negative benefit-risk profile for the proposed indication:

> *ArTiMist 6 is indicated for the initial treatment of severe falciparum malaria in children weighing between 5 and 15 kg. ArTiMist 6 should only be used when therapy with parenteral artesunate is not available.*
>
> *ArTiMist 6 is also indicated for the initial treatment of children weighing between 5 and 15kg with uncomplicated falciparum malaria who cannot tolerate or reliably*

[8] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

take oral medication due to gastrointestinal complications such as vomiting or diarrhoea (Refer Precautions and Contraindications).

Patients started on ArTiMist 6 should receive at least 24 hours treatment (2 doses) and stop as soon as possible thereafter once they are normal per os, and a complete course of artemisinin based combination therapy should be provided (see Dosage And Administration).

In providing this advice the ACM:

- Noted that the sponsor does not intend to market ArTiMist 6 in Australia but is seeking prequalification from a stringent regulatory authority in order to register the proposed product for the treatment of malaria in malaria-endemic countries (for example, Ghana, Ethiopia and Kenya). The sponsor would like ArTiMist 6 to be adopted onto the WHO Guidelines for the Treatment of Malaria.
- Noted that no similar applications have been approved or are planned in any other countries.
- Noted that the WHO does not recommend oral artemisinin monotherapy in the treatment of malaria due to the risk of potentiating treatment resistance.
- Noted that there are currently intramuscular and rectal artemisinin-based formulations available in Africa for pre-referral treatment of falciparum malaria and that the rectal formulations have proven efficacy and safety in young children and their use when intravenous or intramuscular artesunate cannot be given is supported by the WHO.
- Expressed concern that the stability of the proposed product was not tested at higher temperatures comparable to African temperature zones.
- Was of the view that there was insufficient evidence to establish efficacy and safety of ArTiMist 6 and that the potential benefit of a new dosage form did not outweigh the significant risks associated with development of resistance from monotherapy.

Specific Advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. ***Does ACM consider there is a potential role for this sublingual monotherapy product for initial treatment of severe falciparum malaria in young children in endemic countries, given ArTiMist 6 should only be used when therapy with parenteral artesunate is not available? The clinical evaluation report considers that this sublingual treatment could be given by non-medical personnel. The sponsor has committed to an educational program to ensure the product remains within the health care system and does not reach the public domain.***

The ACM noted that the WHO recommendations for pre-referral treatment of severe malaria, in descending order of preference, are: IV artesunate > IM artesunate > rectal artesunate > IM artemether > IM quinine. The patient should then be referred to an appropriate facility for further care and treatment with a longer acting antimalarial agent.

The ACM also noted that the WHO currently supports the development of artemisinin-based combination therapies in preference of artemisinin -based monotherapies due to the risk of potentiating development of resistance.

The role of the proposed product would be in remote rural areas that do not have access to parenteral artesunate and there is potentially a long delay before the patient could reach hospital. In such scenarios, a SL spray may be easier to administer prior to transfer to a hospital and would provide rapid absorption and a higher bioavailability than oral tablets.

However, the ACM advised that a rectal dosage form of artesunate has been available for some years and is readily available in regions across Africa. Additionally, suppositories provide good absorption and are likely to be more stable than a SL spray in relation to the higher temperatures experienced in Africa.

The ACM was of the view that the potential role of a SL artemether monotherapy is not supported by the current WHO recommendations/preference for combination therapy, especially given that there are already alternative effective treatments available in African regions.

2. Has efficacy for the new product been adequately established in the one small pivotal clinical study?

Efficacy data for ArTiMist 6 was provided in the Phase IIa Study ART003 and the pivotal efficacy Study ART004. Study ART004 was a Phase III, randomised, open label, superiority trial of ArTiMist 6 versus IV quinine. The study was conducted in 151 children with severe or complicated falciparum malaria, or children with uncomplicated malaria with GI complications. The small clinical trial program demonstrated efficacy of SL artemether in line with IV quinine.

The ACM was of the view that although artemether is an effective and widely used medication in adults and children, the population group for the single pivotal study was too small to sufficiently demonstrate the efficacy of ArTiMist 6. Additionally, the Study ART004 design, investigator blinding and currency of data (the study was conducted between November 2010 and September 2012) also raised concerns.

3. Has the safety of the product for the new product been adequately established given clinical study program has involved only 93 children?

The ACM noted that there are no safety signals related to the use of artemether and that there is a very large database of literature in favour of its use.

However, the ACM also noted that limited safety information on ArTiMist 6 was provided by the sponsor and no safety pharmacology studies were submitted. Although the clinical trial program for ArTiMist 6 demonstrated safety in a small population, the population size was considered to be too small to be representative.

The ACM was of the view that there was insufficient data to adequately establish the safety of ArTiMist 6.

4. Has the risk of potentiation of resistance associated with this monotherapy product been adequately addressed by changes to draft PI and CMI, and the sponsor's commitments to provide an educational program for health care providers and to work with WHO to minimise this risk?

The ACM advised that *P. falciparum* readily develops resistance to artemisinin monotherapy and resistant strains have been found in parts of South-East Asia. Resistance is slower to develop after the use of artemisinin-based combination therapies (compared to monotherapy).

The WHO recommends use of artemisinin-based combination therapies as development of artemisinin resistance could be potentiated by artemisinin monotherapy. The Worldwide Antimalaria Resistance Network states that a major focus for containing resistance is the cessation of artemisinin-based monotherapy. The WHO Global Malaria Programme has a project in place to phase out the use of oral artemisinin-based monotherapy medicines from the market to limit the emergence and spread of artemisinin-resistance.

Although reasonable measures have been proposed to mitigate the risk of resistance from ArTiMist 6, the risk remains real as the potential for misuse of the monotherapy in malaria-endemic countries cannot be assessed.

The ACM was of the view that it was unnecessary to discuss the PI or CMI given the overall negative risk-benefit profile for the proposed product.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of ArTiMist 6 artemether 6.17 mg/actuation spray solution bottle for the proposed therapeutic indication:

> *ArTiMist 6 is indicated for the initial treatment of severe falciparum malaria in children weighing between 5 and 15kg. ArTiMist 6 should only be used when therapy with parenteral artesunate is not available.*
>
> *ArTiMist 6 is also indicated for the initial treatment of children weighing between 5 and 15kg with uncomplicated falciparum malaria who cannot tolerate or reliably take oral medication due to gastrointestinal complications such as vomiting or diarrhoea (Refer PRECAUTIONS and CONTRAINDICATIONS).*
>
> *Patients started on ArTiMist 6 should receive at least 24 hours treatment (2 doses) and stop as soon as possible thereafter once they are normal per os, and a complete course of artemisinin based combination therapy should be provided (see DOSAGE AND ADMINISTRATION).*

Reasons for the decision

The Delegate has considered the opinion of the ACM, and has made a decision not to register ArTiMist 6 because clinical efficacy and safety of the proposed product have not been adequately established for the proposed indication.

The single pivotal Study ART004 was too small to sufficiently demonstrate the efficacy of ArTiMist 6. Additionally, the Study ART004 design, investigator blinding and currency of data (the study was conducted between November 2010 and September 2012) also raise concerns.

Clinical studies with the proposed product involve only 93 paediatric patients with malaria and provide insufficient data to adequately establish the safety of ArTiMist 6.

The Delegate has also taken into account the potential for *P. falciparum* resistance to artemisinin with an oral monotherapy product and the potential for misuse of the monotherapy in malaria-endemic countries cannot be assessed. The potential role of a SL artemether monotherapy is not supported by the current WHO recommendations / preference for combination therapy, especially given that there are already alternative effective treatments available in African regions.

The Delegate has decided there is an overall negative benefit-risk profile for ArTiMist 6.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The Delegate of the Minister decided to confirm the initial decision on the basis that they are not satisfied that safety and efficacy of the product have been satisfactorily established

for the purpose for which it is proposed to be used. The Delegate of the Minister's reasons for that decision are as follows.

The material in the submission was sufficient to demonstrate superiority of the product compared to IV quinine, at the dose proposed, for the treatment of severe malaria or malaria where oral intake is compromised. Such treatment is now being actively discouraged by the WHO because monotherapy treatment with artemether promotes the development of resistance to artemisinin-based compounds. Should resistance develop in future, the treatment of *P. falciparum* malaria will be severely compromised.

The Delegate of the Minister notes the conclusion of the authors of a Cochrane review referred to by the sponsor that evaluated the role for artemether in severe malaria.[9] The Delegate of the Minister agrees with those authors in that artemether appears to be more effective than quinine in children (with severe malaria) and that artemether is acceptable when artensunate is not available. While this may be so, it is not consistent with current WHO malaria treatment guidelines. The sponsor has contended that it is consistent with the third edition (2015) WHO treatment guidelines;[3] however, those guidelines were referring only to the initial treatment stage where patients were not able to tolerate oral treatments. The initial treatment was to be followed with an ACT. The Delegate of the Minister notes that while some national guidelines may include use of monotherapy treatments for falciparum malaria, these guidelines have not taken into sufficient consideration the potential for the development of resistance of falciparum malaria to a monotherapy treatment, including monotherapy artemether.

The Delegate of the Minister also notes that, consistent with the 2015 WHO guideline on the treatment of malaria,[3] that if artesunate is not available, artemether is recommended in preference to quinine for treating children and adults with severe malaria. While the Delegate of the Minister agrees with this statement, the context was that it applied to the first 24 hours of treatment only and that it referred to parenteral therapy until patients can tolerate oral medication. It was to be followed with complete treatment with 3 days of ACT. That recommendation is not consistent with the proposed dose recommendations for ArTiMist 6, which allow for up to 4 days treatment for children with a body weight of 15 kg and longer for children and infants with lower body weights.

The Delegate of the Minister notes that the Delegate (of the Secretary) had contended the following in their report:

> 'ArTiMist is consistent with WHO recommendations for pre-referral treatment in that i) it is easy to administer and well tolerated, and ii) its bioavailability and thus blood concentrations to which the parasite is exposed are at least those of equivalent oral therapy. The artemisinin drug in ArTiMist is artemether with which there is extensive clinical experience of safety and efficacy; it is simply being administered in a different form and route.'

The Delegate of the Minister considers the above statement to be true however, this does not outweigh the deleterious effects of use of artemether as a monotherapy. In particular, the use of a rectal artemisinin product for pre-treatment of malaria is recommended only for a single dose. Furthermore it is known to be misused and to be contributing to the development of resistance to artemisinins in the treatment of falciparum malaria. The addition of another, easier to use monotherapy artemisinin product containing doses sufficient to provide multiple days of treatment when only a single dose of that type of treatment is currently recommended by the WHO (for pre-referral treatment) is not consistent with the safe use of artemether.

The Delegate of the Minister is of the view that should ArTiMist 6 be made available in areas where there is falciparum malaria, initially it is likely to be efficacious in areas where

[9] Esu, E. B. et al (2019). Artemether for severe malaria, *Cochrane Systematic Review*.

there is no or limited resistance to artemisinins, however that success would be followed by decreasing efficacy over time as resistance develops to artemether and to other products containing artemisinins. Were this resistance to occur there would be a strongly negative risk/benefit balance to the use of ArTiMist 6 for the treatment of falciparum malaria.

The Delegate of the Minister does not consider that it will be possible to restrict uses of ArTiMist 6 to those recommended by the sponsor. To support this view, the Delegate of the Minister notes the following from a published paper referred to by the sponsor.[10] That paper reported significant difference between public and private healthcare workers on adherence to national malaria diagnosis and treatment guidelines. In addition, the publication noted that monotherapy including artesunate (58.3 % versus 12.5 %), amodiaquine (38.9 % versus 8.3 %) and chloroquine (26.4 % versus 4.2 %) were significantly more available in private than public health facilities, respectively. Adherence to guidelines was significantly higher among public healthcare workers (60.6 %) compared to those in private facilities (27.3 %). Additionally, while the Delegate of the Minister notes that [Information redacted], Head of Clinical Research Unit/Principal Investigator, supports use of SL artemether for stabilising patients before being referred for care, the Delegate of the Minister does not consider it will be possible for the proposed education program, monitoring and regulation to prevent misuse of the product in the remote areas where it is proposed to be used. The Delegate of the Minister has formed this view because there is already evidence of misuse of monotherapy rectal artemisinin derivatives;[11] beyond its recommended purpose and ArTiMist, containing multiple doses per bottle and being easier to administer, is likely to be more prone to misuse, particularly in the treatment of suspected malaria and malaria which is not severe.

Given the low adherence to national or treatment guidelines the Delegate of the Minister considers it is likely that adherence to the indications and dosage recommendations for ArTiMist 6 will have a similar low level of compliance and its use would provide an additional avenue for exposure to monotherapy artemisinin in patients with falciparum malaria. This will increase the likelihood of resistance to artemisinins, including artemether developing in these populations.

The Delegate of the Minister notes that the sponsor recognises the importance of the WHO Malaria Treatment Guidelines, and the need to ensure that the risk of resistance to artemisinins is minimised. To this effect it was proposed that the primary use of the product would be for patients prior to embarking on the critical journey between a rural community setting and an appropriately equipped treatment centre where artemisinin-based combination therapies can be administered. The bottle contains 50 doses, which is sufficient for patients with a body weight of 15 kg, the maximum recommended body weight for use of the product, to receive 7 doses. Following the proposed dose regimen of a dose at 0, 8, 24, 36, 48, 60, then every 24 hours, this would be 84 hours of treatment. Longer treatment durations would be possible for children with lower body weights. In Delegate of the Minister's view, such excess supply of the product in each bottle is likely to encourage use beyond the recommended initial period prior to transfer to a treatment facility.

As noted in the WHO document on the use of rectal artesunate for pre-referral treatment of severe malaria;[11] access to treatment is still poor in many areas, and the rational use of rectal artesunate is key to reducing mortality due to severe malaria and at the same time to preserving artemisinins from the risk that resistance to them will develop. This would have devastating consequences on people's health in malaria-endemic countries and could

[10] Bamiselu, O.F. et al (2016). Adherence to malaria diagnosis and treatment guidelines among healthcare workers in Ogun State, Nigeria, BMC Public Health, 2016; 16: 828
[11] Global Malaria Programme, Rectal artesunate for pre-referral treatment of severe malaria, October 2017 (Rev. October 2018).

reverse the progress in malaria control achieved in many countries over the past decade. No alternative medicines are ready to enter the market in the next few years that could replace ACTs, the mainstay of treatment for malaria.

The Delegate of the Minister notes that the sponsor has proposed an education program for healthcare workers in the areas in which the product would be marketed. However, given the reported lack of adherence to treatment recommendations published by the WHO and to national guidelines it is not evident to the Delegate of the Minister that this program would be successful.

Efficacy and safety of the product as an initial treatment for severe malaria in children prior to embarking on the critical journey between a rural community setting and an appropriately equipped treatment centre where artemisinin combination therapy can be administered has not been assessed in a clinical trial. The pivotal clinical trial involved a complete monotherapy treatment course of either ArTiMist or IV quinine however the indications proposed limit use to initial treatment.

There are available treatments for an initial treatment where children are unable to take oral medication. A single IM dose of artesunate or a single rectal dose of artesunate (in children aged < 6 years) are alternatives recommended in the 2015 edition of the WHO Guidelines for the treatment of malaria.[3] The Delegate of the Minister notes these are single doses and considers it likely that these single doses would be less likely to lead to the development of resistance than a product containing a minimum of 84 hours of monotherapy treatment which is relatively easy to administer.

In giving consideration to the safety and efficacy of a product for its intended purpose the Delegate of the Minister has considered not only efficacy and safety in individual patients on initial approval but have also considered the impact of use of the product in patients with falciparum malaria as a whole. The Delegate of the Minister finds that this product is likely to lead to a reduction in efficacy of artemisinin-based anti-malarial products, including this product, in areas in which it is used. Furthermore, efficacy for the primary intended purpose of initial treatment prior to transfer to a treatment facility has not been assessed.

Conclusion

For the reasons outlined above, the Delegate of the Minister has decided to confirm the initial decision on the basis that they are not satisfied that the safety and efficacy of the product have been satisfactorily established for the purpose for which it is proposed to be used.

The Delegate of the Minister further considers that the product should not be registered because of the significant likelihood that the product will lead to a broader reduction in the efficacy of artemisinin-based anti-malarial products due to the potentiation of disease resistance.

Outcome from appeal to the Administrative Appeals Tribunal

The sponsor appealed to the Administrative Appeals Tribunal (AAT) for review of the TGA's decision not to register Artemether.

The sponsor later withdrew their application to the AAT.

Therapeutic Goods Administration

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