22 November 2021
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EMADOC-1700519818-734311
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Artesunate Amivas (artesunate)
Treatment of malaria
EU/3/20/2251

Sponsor: Amivas Ireland Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Artesunate
Other name(s)	Artesunate Applicant claims that product is not the same as https://adisinsight.springer.com/drugs/800053728
International Non-Proprietary Name	Artesunate
Tradename	Artesunate Amivas
Orphan condition	Treatment of malaria
Sponsor's details:	Amivas Ireland Limited Durands Court 7 Parnell Street Waterford X91 P381 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Yes Pharmaceutical Development Services GmbH
COMP opinion	22 January 2020
EC decision	28 February 2020
EC registration number	EU/3/20/2251
Post-designation procedural history	
Transfer of sponsorship	Transfer from Yes Pharmaceutical Development Services GmbH to Amivas Ireland Limited – EC decision of 4 September 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jayne Crowe / Johann Lodewijk Hillege
Applicant	Amivas Ireland Limited
Application submission	14 September 2020
Procedure start	1 October 2020
Procedure number	EMA/H/C/0005550
Invented name	Artesunate Amivas
Therapeutic indication	Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children (see sections 4.2 and 5.1). Consideration should be given to official guidance on the appropriate use of antimalarial agents. Further information on Artesunate Amivas can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/ArtesunateAmivas
CHMP opinion	16 September 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Elisabeth Johanne Rook
Sponsor's report submission	26 April 2021
COMP discussion	5-7 October 2021
COMP opinion	7 October 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

"The sponsor YES Pharmaceutical Development Services GmbH submitted on 10 October 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing artesunate for treatment of malaria (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing artesunate was considered justified based on clinical data showing efficacy in severe malaria;
- the condition is life-threatening due to the possibility of severe systemic complications such as cerebral malaria, cardiogenic shock, acute renal failure, coagulation disorders and pulmonary oedema. The overall mortality rate of imported Plasmodium falciparum malaria in Europe is 0.4%;
- the condition was estimated to be affecting approximately 0.12 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing artesunate will be of significant benefit to those affected by the condition. This appears justified by the improved clinical efficacy of artesunate administered intravenously as monotherapy in the treatment of severe malaria as compared to quinine, the only currently authorized product for intravenous use in the EU. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing artesunate as an orphan medicinal product for the orphan condition: treatment of malaria."

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Malaria is caused by protozoan pathogens of the Plasmodium spp.; Plasmodium falciparum and Plasmodium vivax, for which humans are the exclusive mammalian hosts. These are the most common species and are responsible for the largest public health burden. Malaria is transmitted by the bite of Plasmodium spp.-infected female mosquitoes of the Anopheles genus. During a blood meal, infected mosquitoes inject — along with their anticoagulating saliva — sporozoites, which are the infective, motile stage of Plasmodium spp. Sporozoites journey through the skin to the lymphatics and into hepatocytes in the liver. Inside the hepatocyte, a single sporozoite can generate tens of thousands of merozoites (the stage that results from multiple asexual fissions (schizogony) of a sporozoite within the body of the host), which are released into the bloodstream where they enter red blood cells to replicate (erythrocytic schizogony). A fraction of merozoites (those that are sexually committed) also differentiate and mature into male and female gametocytes, which is the stage that infects the mosquito host when it takes a blood meal. The onset of clinical symptoms generally occurs 7–10 days after the initial mosquito bite.

- Asymptomatic malaria: can be caused by all *Plasmodium* spp.; the patient has circulating parasites but no symptoms.
- Uncomplicated malaria: can be caused by all *Plasmodium* spp. Symptoms are nonspecific and can include fever, moderate-to-severe shaking chills, profuse sweating, headache, nausea, vomiting, diarrhea and anaemia, with no clinical or laboratory findings of severe organ dysfunction.
- Severe (complicated) malaria: usually caused by infection with *Plasmodium falciparum*, although less frequently it can also be caused by *Plasmodium vivax* or *Plasmodium knowlesi*. Complications include severe anaemia and end-organ damage, including coma (cerebral malaria), pulmonary complications (for example, oedema and hyperpnoea syndrome), and hypoglycaemia or acute kidney injury. Severe malaria is often associated with hyperparasitaemia and is associated with increased mortality.

The approved therapeutic indication "Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children (see sections 4.2 and 5.1). Consideration should be given to official guidance on the appropriate use of antimalarial agents." Falls within the scope of the designated orphan condition "treatment of malaria".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There has been no change in the chronically debilitating and life-threatening nature of the condition.

Typical initial symptoms are low-grade fever, shaking chills, muscle aches and, in children, digestive symptoms. These symptoms can present suddenly (paroxysms), and then progress to drenching sweats, high fever and exhaustion. Malaria paroxysmal symptoms manifest after the haemolysis of Plasmodium spp.-invaded red blood cells.

Severe malaria is often fatal and presents with severe anaemia and various manifestations of multi-organ damage, which can include cerebral malaria. Severe malaria complications are due to microvascular obstruction caused by the presence of red blood cell stage parasites in capillaries. By this stage of the disease, the case fatality in people receiving treatment is typically 10–20%. However,

if left untreated, severe malaria is fatal in the majority of cases (WHO, 2010). In adults, severe malaria caused by P. falciparum is characterized by multiorgan damage, whereas children with severe malaria usually present with prostration, respiratory distress, severe anaemia, and/or cerebral malaria.

For the EU patient of particular concern are the immunological naivety to the parasite and the potential diagnostic delay, which both may enhance the risk of a severe course and fatal outcome.

Number of people affected or at risk

The sponsor has provided data from "The European Surveillance System (TESSy)". This system collects, analyses, and disseminates data on communicable diseases, and has annual epidemiological data on malaria for 30 EU/EEA countries published by the European Centre for Disease Prevention and Control (ECDC). Annual surveillance reports are available for 2013-2017 which indicate that there were 8,401 cases of malaria reported in the EU/EEA in 2017. It can be concluded that the overall incidence of malaria in the EU in 2017 was 1.2 cases per 100,000.

Table 1: Number of malaria cases and rates by country for 2016 to 2018, EU/EEA (European Centre for Disease Prevention and Control 2020)

Country	2016		2017		2018	
	Number	Rate	Number	Rate	Number	Rate
Austria	82	0.9	78	0.9	62	0.7
Belgium	311	-	249	-	357	-
Bulgaria	28	0.4	8	0.1	8	0.1
Croatia	4	0.1	10	0.2	2	0.0
Cyprus	1	0.1	8	0.9	4	0.5
Czech Republic	38	0.4	27	0.3	34	0.3
Denmark	102	1.8	94	1.6	64	1.1
Estonia	1	0.1	2	0.2	3	0.2
Finland	47	0.9	36	0.7	34	0.6
France	2447	-	2712	-	2840	0

Germany	961	1.2	956	1.2	896	1.1
Greece	121	1.1	107	1.0	55	0.5
Hungary	17	0.2	12	0.1	17	0.2
Iceland	2	0.6	3	0.9	3	0.9
Ireland	88	1.9	78	1.6	60	1.2
Italy	888	1.5	830	1.4	722	1.2
Latvia	3	0.2	1	0.1	4	0.2
Liechtenstein	ND	ND	ND	ND	ND	ND
Lithuania	3	0.1	6	0.2	6	0.2
Luxembourg	5	0.9	11	1.9	13	2.2
Malta	7	1.6	12	2.6	7	1.5
Netherlands	245	1.4	202	1.2	252	1.5
Norway	75	1.4	61	1.2	54	1.0
Poland	38	0.1	27	0.1	28	0.1
Portugal	197	1.9	93	0.9	102	1.0
Romania	21	0.1	15	0.1	18	0.1
Slovakia	4	0.1	1	0.0	3	0.1
Slovenia	6	0.3	11	0.5	3	0.1
Spain	755	1.6	824	1.8	851	1.8
Sweden	154	1.6	150	1.5	189	1.9
United Kingdom	1574	2.4	1777	2.7	1656	2.5
EU/EEA	8225	1.2	8401	1.2	8347	1.2

Abbreviations: ND: No data; -: not calculated.

A literature search was also conducted using the PubMed database (US National Library of Medicine and National Institutes of Health; https://www.ncbi.nlm.nih.gov/pubmed) using the search parameters "malaria" and "epidemiology" and "Europe" or "incidence" or "prevalence". The search resulted in 173 publication dated within the last five years (19 March 2016 to 19 March 2021). The date range was selected to yield the most relevant epidemiological data. The titles and abstracts were reviewed to identify publications providing relevant data on the epidemiology of malaria in the EU. Of the 173 results, there were no new epidemiological studies designed for calculating the incidence of malaria in Europe.

The final proposed number by the sponsor is 0.12 in 10,000 which was endorsed by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Chloroquine, amodiaquine, primaquine sulfadoxine-pyrimethamine, mefloquine, atovaquone-proguanil, quinine, doxycycline, and artemisinin derivatives are authorised in Member States for the treatment or prevention of malaria. Eurartesim (piperaquine tetraphosphate / artenimol) has a centralised marketing authorisation.

The WHO provides more detailed guidelines in the management and treatment of severe malaria. Based on high-quality evidence, a strong recommendation of intravenous or intramuscular artesunate is prescribed by the WHO for at least 24 hours until oral medication can be tolerated, at which point 3 days of artemisinin-based combination therapy (add a single dose of primaquine in areas of low transmission) is recommended to complete the treatment regimen.

Table 2: Authorized treatments for the treatment or prophylaxis of malaria in the EU.

Active substance	**Type of authorisation**	**Authorized indication**
Artemether/ lumefantrine (Riamet)	MR procedure (SE/H/1778/001)	Riamet is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults, children and infants of 5 kg and above.
Atovaquone/proguanil hydrochloride (Various generic products, e.g. Malarone)	Various MR procedure	Atovaquone/Proguanil Hydrochloride is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide and also has activity against hepatic schizonts of Plasmodium falciparum. It is indicated for: • Prophylaxis of Plasmodium falciparum malaria in adults and in children weighing more than 40 kg. • Treatment of acute, uncomplicated Plasmodium falciparum malaria in adults and in children weighing 11 kg or more. […]
Chloroquine (phosphate)* (Various products)	Various national authorisations	Prophylaxis, suppression and treatment of malaria. [...]
Dapsone (Various generic products)	Various national authorisations	Prophylaxis of malaria in combination with pyrimethamine
Dihydroartemisinin, piperaquine tetraphosphate (Eurartesim)	Centralized procedure (EU/1/11/716)	Eurartesim is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.
Doxycycline hyclate (Various products)	Various national authorisations	Doxycycline capsules are used in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms. Chloroquine-resistant falciparum malaria […]

Active substance	Type of authorisation	Authorized indication
		Doxycycline is indicated for prophylaxis in the following conditions: […] malaria
Mefloquine (e.g. Lariam)	Various national authorisations	Lariam is especially indicated for therapy of *P. falciparum* malaria in which the pathogen has become resistant to other antimalarial agents. Following treatment of *P. vivax* malaria with Lariam, relapse prophylaxis with an 8- amino-quinoline derivative, for example primaquine, should be considered in order to eliminate parasites in the hepatic phase. [...].
Proguanil hydrochloride (e.g. Paludrine)*	Various national authorisations	Paludrine is an effective antimalarial agent. It is recommended for the prevention and suppression of malaria.
Quinine sulfate (Various generic products)	Various national authorisations	Treatment of falciparum (malignant tertian) malaria.
Quinine hydrochloride (Various generic products	National authorisations (e.g. Quinine Renaudin)	Treatment of severe malaria ("accès pernicieux")

* There are also combination travel packs containing proguanil and chloroquine tablets (e.g. Savarine in France)

Of the above product only, the following are targeting the same patient population as Artesunate Amivas and therefore considered satisfactory methods for "initial treatment of severe malaria caused by *Plasmodium falciparum":*

- Quinine sulfate.
- Quinine hydrochloride.

Significant benefit

Currently IV Quinine (SURQUINA) is only licenced in France to treat patients with severe life-threatening forms of malaria.

No scientific advice or protocol assistance on the product development was sought.

IV artesunate has been shown to be clinically superior to quinine in two published pivotal efficacy studies (AQUAMAT and SEAQUAMAT) in the treatment of severe or complicated malaria, for which IV treatment is essential until oral therapy can be tolerated. Further, IV AS is the first-line recommended product in the treatment of severe or complicated malaria by the WHO.

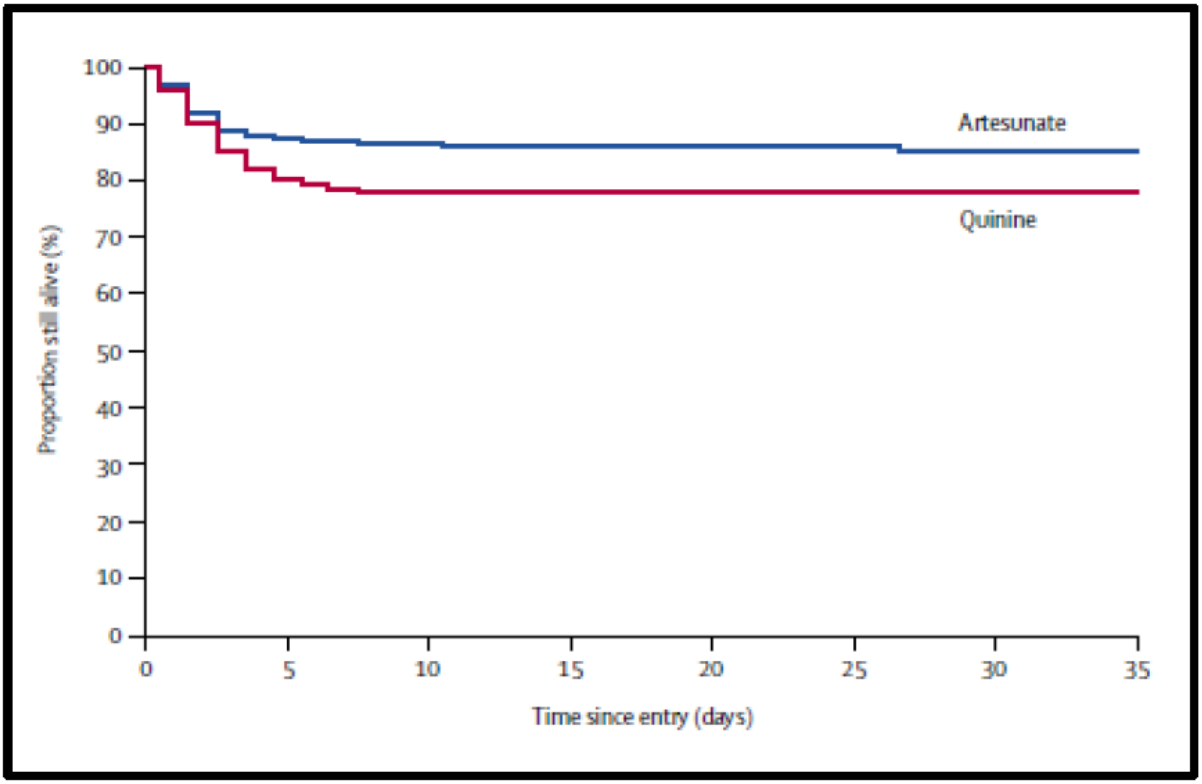
SEAQUAMAT

This randomized study compared the efficacy of parenteral AS (IV AS) to parenteral quinine (IV quinine) in Asian adults using the Guilin Pharmaceuticals (Shanghai) Co., Ltd. IV AS formulation. Patients were randomised to receive IV AS 2.4 mg/kg on admission, then at 12 h, 24 h, and thereafter once daily until oral medication could be taken reliably: oral artesunate 2 mg/kg per day to complete a total course (including parenteral treatment) of 7 days, providing a total cumulative dose of 17–18 mg/kg, or quinine dihydrochloride in a 20 mg/kg loading dose was infused over 4h, followed by 10 mg/kg infused three times a day until starting oral therapy, which consisted of oral quinin 10 mg/kg every 8 h to provide a total quinin course of 7 days.

Parenteral artesunate was shown to reduce mortality in patients with severe malaria by over a third compared with parenteral quinine. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (p=0.0002). Although there were considerable differences in the intensive-care support available between the trial sites, this large reduction in mortality was consistent across countries and in all prospectively defined subgroups.

Retrospectively, SEAQUAMAT patients were classified as "severe" or "non-severe" at entrance. For the "severe" malaria patients, mortality was 20% in the AS group vs. 28% in the quinine group (p = 0.003). For all SEAQUAMAT patients, the benefits of artesunate were most evident after 48 hrs of study entrance.

Figure 1. Survival Curve of In-Hospital Mortality – SEAQUAMAT (Dondorp 2005)



Subjects either died in the hospital or were discharged, so all deaths included. Survival time of all discharged subjects was set to 35 days.

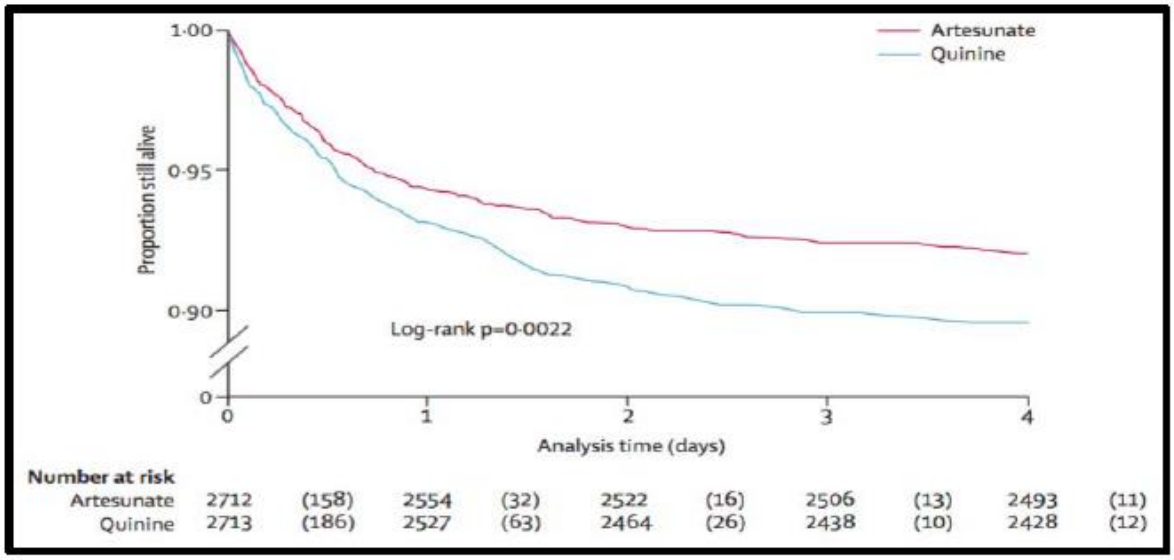
AQUAMAT

This multi-centre, open-label trial conducted in African children with severe malaria randomised 5,306 eligible patients with either parenteral artesunate (Guilin formulation) or parenteral quinine. Artesunate was given in a dose of 2.4 mg/kg on admission, 12 h, 24, h, and thereafter once daily, either as a bolus into an indwelling IV cannula, or administered by deep IM injection, until oral medication could be taken reliably. Quinine dihydrochloride was given in a 20 mg salt per kg loading dose infused over 4 h (in 5-10 mL/kg of 5% dextrose), followed by a 10 mg salt per kg infusion over 2h to 8h three times daily until starting oral therapy. For IM treatment, the doses were the same as for IV treatment; quinine was diluted in normal saline to a concentration of 60 mg/mL and injected into the anterior thigh. The loading dose was given as a split dose into each thigh. When the patient was able to take tablets, but after a minimum of 24 h of parenteral treatment, oral artemether-lumefantrine in a full standard dose (1.5/9 mg/kg twice daily for 3 days with milk or fat) was given to complete the treatment.

The results show parenteral artesunate substantially reduces the overall mortality of African children diagnosed with severe malaria. Two hundred thirty (8.5%) patients assigned to artesunate treatment died compared with 297 (10.9%) assigned to quinine treatment (OR stratified for study site 0.75, 95% CI 0.63–0.90; relative reduction 22.5%, 95% CI 8.1–36.9; p=0.0022). Incidence of neurological sequelae did not differ significantly between groups, but the development of coma (65/1832 (3.5%) with artesunate vs 91/1768 (5.1%) with quinine; p=0.02), convulsions (224/2712 (8.3%) vs. 273/2713 (10.1%); p=0.02), and deterioration of the coma score (166/2712 (6.1%) vs. 208/2713 (7.7%); p=0.02) were each significantly less frequent in artesunate recipients than in quinine recipients.

Similar to SEAQUAMAT trial findings, the benefits of artesunate were more evident after the 1st day of treatment (2.7% for AS vs. 4.2% for quinine) than in the 1st day of treatment (5.8% for AS and 6.9% for quinine).

Figure 2. Kaplan-Meier Curves Comparing Survival in African Children with Severe *P. falciparum* Malaria Treated with Either Parenteral Artesunate or Quinine (AQUAMAT Trial; Dondorp 2010)



The significant benefit of Artesunate Amivas has been established based on an improved efficacy as compared to the only other satisfactory method, intravenous quinine.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 7 October 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of malaria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.12 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to the possibility of severe systemic complications such as cerebral malaria, cardiogenic shock, acute renal failure, coagulation disorders and pulmonary oedema. The overall mortality rate of imported *Plasmodium falciparum* malaria in Europe can reach 7% in the severe forms;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Artesunate Amivas may be of potential significant benefit still holds. When the product was used as induction therapy according to the therapeutic indication, a reduction in mortality due to severe *Plasmodium falciparum* malaria as compared to IV quinine was shown.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Artesunate Amivas (artesunate) for treatment of malaria (EU/3/20/2251) is not removed from the Community Register of Orphan Medicinal Products.