Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Artesunate Amivas 110 mg powder and solvent for solution for injection

artesunate

PLGB 55184/0002

Amivas Ireland Ltd

LAY SUMMARY

Artesunate Amivas 110 mg powder and solvent for solution for injection
Artesunate

This is a summary of the Public Assessment Report (PAR) for Artesunate Amivas 110 mg powder and solvent for solution for injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Artesunate Amivas in this lay summary for ease of reading.

For practical information about using Artesunate Amivas, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Artesunate Amivas and what is it used for?
This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 16 September 2021 (EMEA/H/C/005550/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

Artesunate Amivas is used to treat severe malaria in adults and children. After treatment with Artesunate Amivas, as instructed by their doctor, patients will complete their treatment for malaria with a course of anti-malarial medication that can be taken by mouth.

How does Artesunate Amivas work?
Artesunate Amivas contains the active substance artesunate. Its exact mode of action is not fully understood, but once it has entered blood cells infected by the malaria parasite, the medicine is thought to form toxic substances called ‘free radicals’ that kill the parasite.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

How is Artesunate Amivas used?
The pharmaceutical form of this medicine is powder and solvent for solution for injection and the route of administration is slow injection directly into a vein (intravenous injection)

This medicine will be given by slow injection directly into a vein. The doctor or nurse will inject this medicine. The doctor or nurse will work out the right amount (dose) to give their patient. The recommended dose is 2.4 mg for each kg of body weight. The dose per kg is the same for adults and children of all ages.

Patients will be given at least three doses of Artesunate Amivas, each dose is to be given 12 hours apart. After three doses, if the patient remains unable to take medicines by mouth, they will be given one dose of Artesunate Amivas every 24 hours (once a day) until they are able to take a different malaria treatment by mouth.

After taking at least three doses of Artesunate Amivas by injection, it is very important that patients complete a full course of antimalarial treatment taken by mouth

For further information on how Artesunate Amivas is used, refer to the PIL and Summary of Product Characteristic (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of intravenous Artesunate Amivas have been shown in studies?
Two main studies showed that initial treatment with injectable artesunate was more effective than that with another malaria medicine, quinine, in reducing the risk of death in hospitalised patients with severe malaria.

The first study involved 1,461 adults and children. Patients received injectable treatment until they were able to receive treatment by mouth, either with intravenous Artesunate Amivas or with quinine. The results showed that 107 out of 730 (14.7%) patients who received initial treatment with intravenous Artesunate Amivas died in hospital compared with 164 out of 731 (22.4%) of those who received initial treatment with quinine.

In the second study, which involved 5,425 children under 15 years of age hospitalised with malaria, 230 out of 2712 (8.5%) patients who received intravenous Artesunate Amivas by injection followed by treatment with the malaria medicine artemether-lumefantrine died in hospital compared with 297 out of 2713 (10.9%) of those who received quinine by injection followed by artemether-lumefantrine.

What are the possible side effects of Artesunate Amivas?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Artesunate Amivas (which may affect more than 1 in 10 people) are a lack of healthy red blood cells, which can make the patient feel tired and weak (anaemia); this can develop at least 7 days or sometimes several weeks after treatment has finished.

Why was Artesunate Amivas approved?
MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Artesunate Amivas has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Artesunate Amivas?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Artesunate Amivas The RMP details the important risks of Artesunate Amivas, how these risks can be minimised, any uncertainties about Artesunate Amivas (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Artesunate Amivas:

Important identified risks: None
Important potential risks: Reproductive toxicity (especially in the first trimester)
Missing information: None

There are no additional risk minimisation activities, however, additional pharmacovigilance activities include a pregnancy registry, and a non-clinical - animal study, for further details of these activities please refer to section VI. Risk Management Plan (RMP) of this report.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Artesunate Amivas are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and these documents are satisfactory.

Other information about Artesunate Amivas
A marketing authorisation was granted in Great Britain on 29 April 2022.

The full PAR for Artesunate Amivas follows this summary.

This summary was last updated in June 2022.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Artesunate Amivas 110 mg powder and solvent for solution for injection (PLGB 55184/0002) could be approved.

The product is approved for the following indications:
Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children. Consideration should be given to official guidance on the appropriate use of antimalarial agents.

Mechanism of action
The antimalarial mechanism of action of artesunate is generally thought to depend upon activation involving iron-mediated cleavage of the endoperoxide bridge of DHA to generate an unstable organic free radical followed by alkylation, where the free radical binds to malarial proteins leading to destruction of parasite membranes.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 16 September 2021 (EMEA/H/C/005550/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended).

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM) on 6 March 2022. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP), PIP P/0328/2020. At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and these documents are satisfactory.

A Marketing Authorisation was granted on 29 April 2022.

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

V. CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Important potential risk: Reproductive Toxicity (especially in the first trimester)	
Evidence for linking the risk to the medicine	Early embryotoxicity has been seen in several animal species. However, there are only limited clinical data on IV artesunate use in the first-trimester of pregnancy. A recent study showed no evidence that the artemisinin-associated embryotoxicity observed in cross-species animal models (embryolethality and congenital anomalies) was present in human pregnancies. The available data provide no evidence of an increased risk of miscarriage or stillbirth among pregnancies with a confirmed first-trimester artemisinin treatment compared to pregnancies with quinine or no antimalarial treatment [Dellicour, 2017].
Risk factors and risk groups	Women taking IV artesunate, especially in the first trimester of pregnancy.
Risk minimisation measures	Routine risk communication: Section 4.6 and 5.3 of the SmPC and section 2 of the PIL. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Pack size: Each box contains 2 vials of Artesunate Amivas powder and 2 vials of phosphate buffer. Three boxes (6 vials) are enough for 3 doses of 2.4 mg/kg for a person up to 91.3 kg. Legal status: Restricted medical prescription.
Additional pharmacovigilance activities	Intravenous Artesunate Pregnancy Registry See section II.C of this summary for an overview of the post-authorisation development plan. Intravenous Injection Fertility and Early Embryonic Development Study of Artesunate in Sprague Dawley Rats. See section II.C of this summary for an overview of the post-authorisation development plan.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

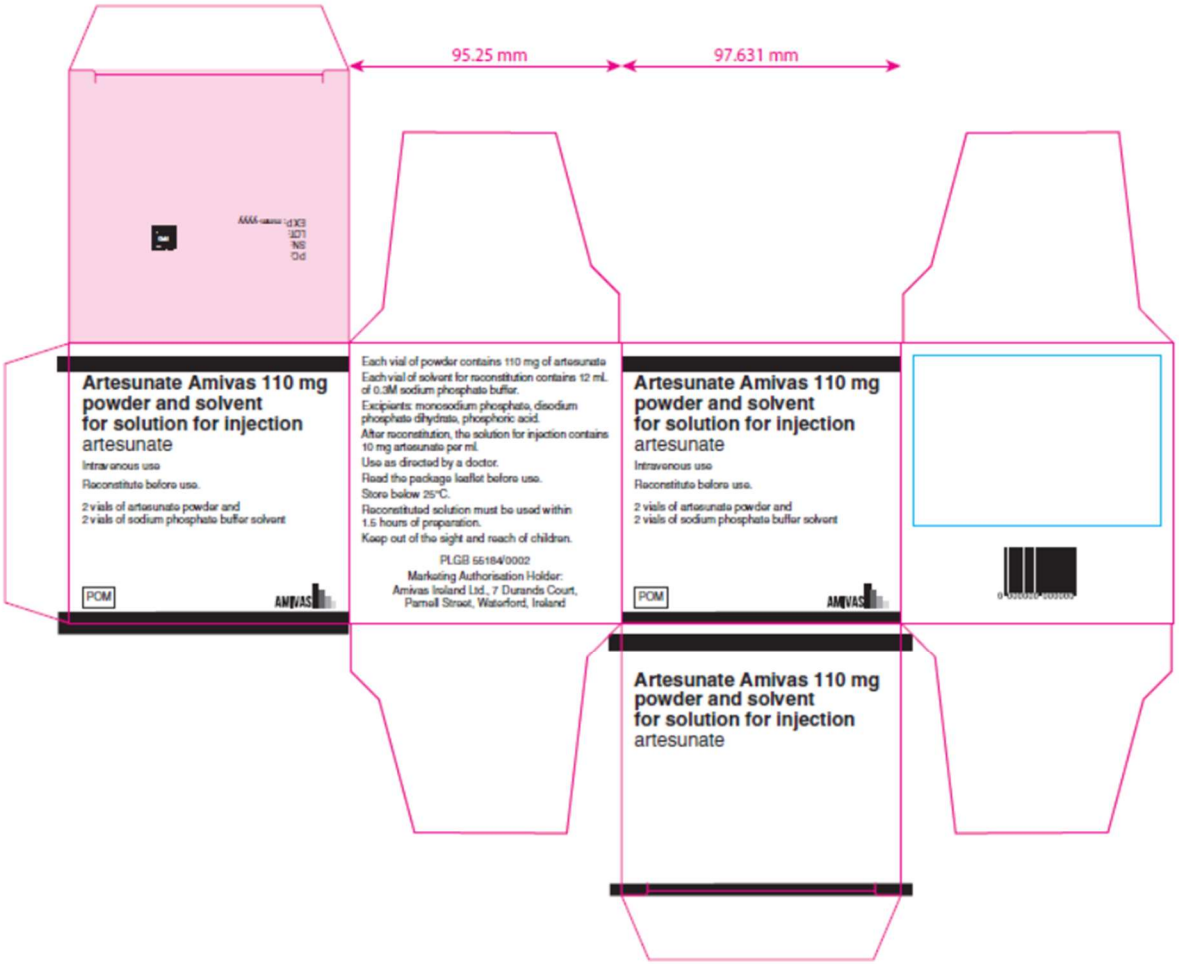
VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

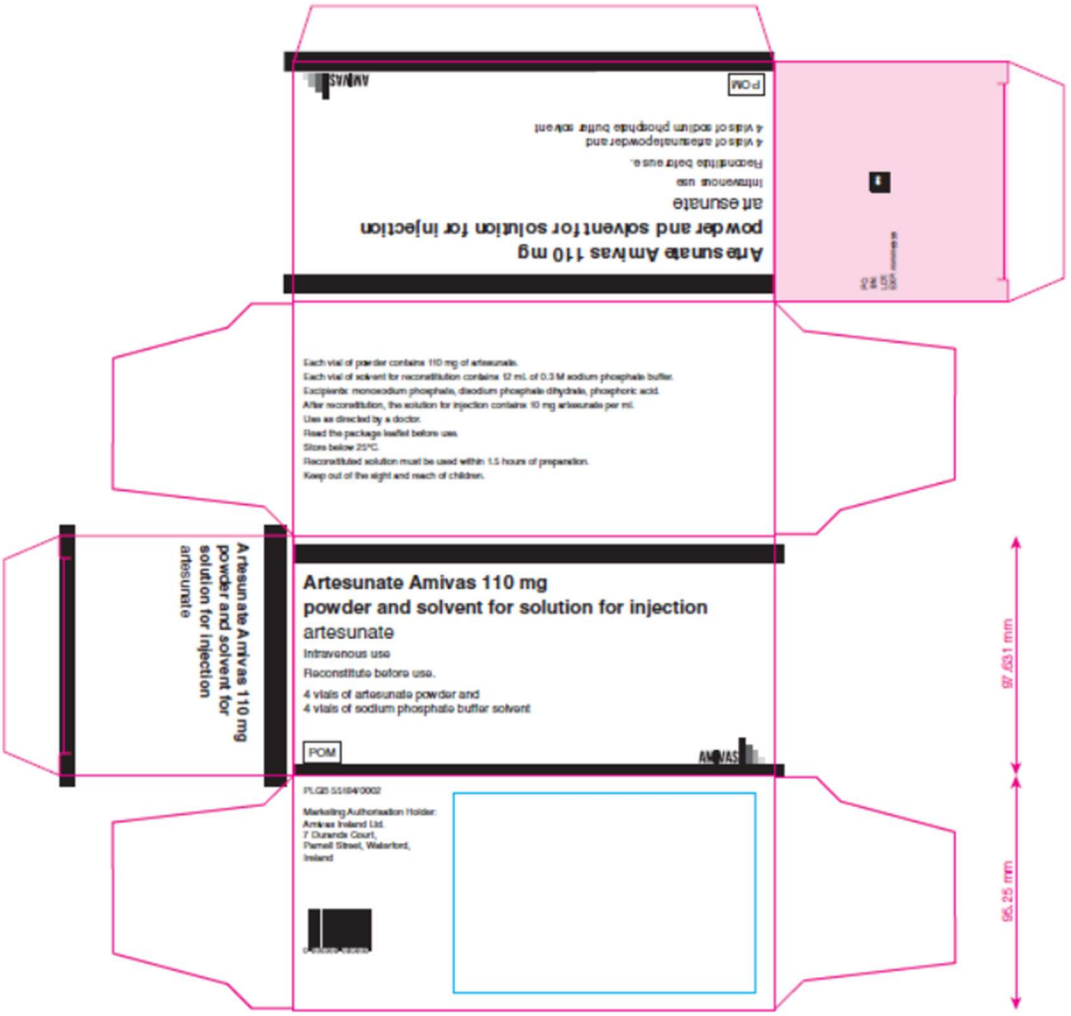
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

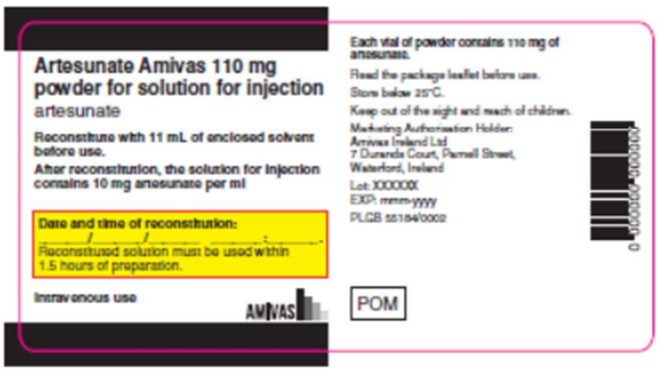
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

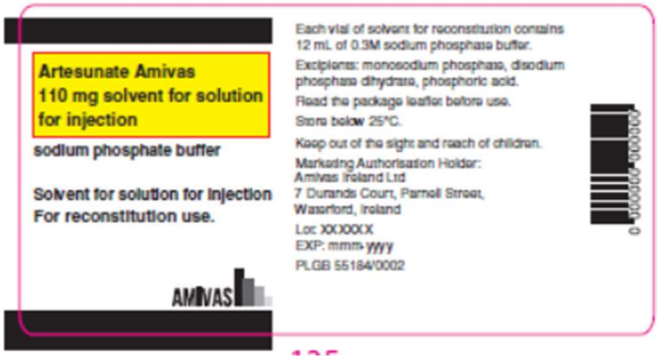
In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.




Each vial of powder contains 110 mg of artesunate.
Each vial of solvent for reconstitution contains 12 mL of 0.3 M sodium phosphate buffer.
Excipients: monosodium phosphate, disodium phosphate dihydrate, phosphoric acid.
After reconstitution, the solution for injection contains 10 mg artesunate per ml.
Use as directed by a doctor.
Read the package leaflet before use.
Store below 25°C.
Reconstituted solution must be used within 1.5 hours of preparation.
Keep out of the sight and reach of children.
Artesunate Amivas 110 mg
powder and solvent for solution for injection
artesunate
Intravenous use
Reconstitute before use.
4 vials of artesunate powder and
4 vials of sodium phosphate buffer solvent
POM
PLGB 55184/0002
Marketing Authorisation Holder:
Amivas Ireland Ltd.
7 Durands Court,
Parnell Street, Waterford,
Ireland
97.631 mm
95.25 mm


Artesunate Amivas 110 mg
powder for solution for injection
artesunate
Reconstitute with 11 mL of enclosed solvent before use.
After reconstitution, the solution for injection contains 10 mg artesunate per ml
Date and time of reconstitution:
Reconstituted solution must be used within 1.5 hours of preparation.
Intravenous use
Each vial of powder contains 110 mg of artesunate.
Read the package leaflet before use.
Store below 25°C.
Keep out of the sight and reach of children.
Marketing Authorisation Holder:
Amivas Ireland Ltd
7 Durands Court, Parnell Street,
Waterford, Ireland
Lot: XXXXXX
EXP: mmm-yyyy
PLGB 55184/0002
POM


Artesunate Amivas
110 mg solvent for solution for injection
sodium phosphate buffer
Solvent for solution for injection
For reconstitution use.
Each vial of solvent for reconstitution contains 12 mL of 0.3M sodium phosphate buffer.
Excipients: monosodium phosphate, disodium phosphate dihydrate, phosphoric acid.
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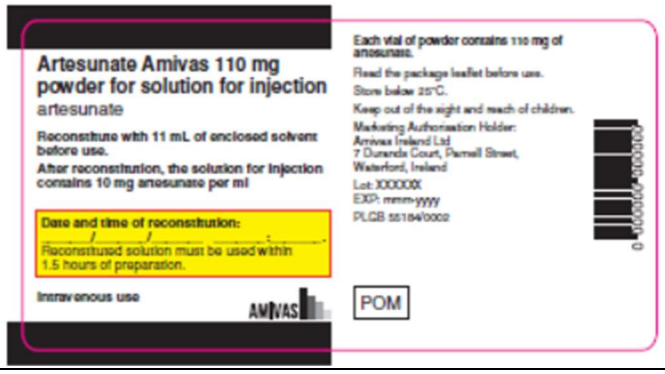
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7 Dunareis Court, Parnell Street,
Waterford, Ireland
Lot: XXXXXX
EXP: mmm-yyyy
PLGB 55184/0002
POM

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Product: Artesunate Amivas 110 mg powder and solvent for solution for injection
Active substance: artesunate
Orphan Designation Number: *PLGB 55184/0002/OD1*

Background:

This application was evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled.

Evaluation:

Orphan condition
The orphan condition is malaria. This is acceptable and in line with the guidance on what constitutes a valid condition.

Malaria is a recognised distinct medical condition with defined pathophysiological and clinical characteristics. These characteristics determine the group of patients in whom development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions. Different degrees of severity or stages of a disease would generally not be considered as distinct conditions.

Orphan indication
The orphan indication is: Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children. Consideration should be given to official guidance on the appropriate use of antimalarial agents

Life threatening/ debilitating condition
Malaria can be a severe and seriously debilitating and if left untreated, could be life-threatening. It can affect many different organ systems such as nervous, pulmonary, renal etc. and rapidly progress to serious sequelae and early death due to the consequences.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects 0.3 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of diagnosis/prevention/ treatment
Treatment of malaria is based on a number of different drugs as recommended by WHO/ international/ national/ local guidelines. Early diagnosis is important for early intervention. Preventative modalities can include both pharmacological and non-pharmacological options.

Justification of significant benefit
Artesunate showed improved efficacy as compared to the only other satisfactory method, intravenous quinine. The safety profile is also considered acceptable in the population specified by the indication.

Overall, it is considered that significant benefit has been demonstrated in the proposed target population.

Conclusion on acceptability of orphan designation
The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 29 April 2022