Part VI: Summary of the risk management plan

Summary of risk management plan for Artesunate Amivas, 110 mg, powder and solvent for solution for injection (artesunate)

This is a summary of the risk management plan (RMP) for Artesunate Amivas, 110 mg, powder and solvent for solution for injection (hereinafter referred to as Artesunate Amivas). The RMP details important risks of Artesunate Amivas, how these risks can be minimised, and how more information will be obtained about Artesunate Amivas's risks and uncertainties (missing information).

Artesunate Amivas's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Artesunate Amivas should be used.

This summary of the RMP for Artesunate Amivas should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Artesunate Amivas's RMP.

I. The medicine and what it is used for

Artesunate Amivas is authorised for the initial treatment of severe malaria, in adults and children (see SmPC for the full indication). It contains artesunate as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of Artesunate Amivas's benefits can be found in Artesunate Amivas's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/artesunate-amivas).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Artesunate Amivas, together with measures to minimise such risks and the proposed studies for learning more about Artesunate Amivas's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Artesunate Amivas are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Artesunate Amivas. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Reproductive toxicity (especially in the first trimester)
Missing information	None

II.B Summary of important risks

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.
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)

Important potential risk: Reproductive Toxicity (especially in the first trimester)	
	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.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Artesunate Amivas.

II.C.2 Other studies in post-authorisation development plan

Intravenous Artesunate Pregnancy Registry

Purpose of the study: the purpose of this observational study is to fulfil FDA and EMA Post Marketing Requirements The study will be a single-arm descriptive international study collecting data in women exposed to IV artesunate during pregnancy to assess risk of pregnancy and maternal complications and adverse effects on the foetus, neonate, and infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for 7 years.

Intravenous Injection Fertility and Early Embryonic Development Study of Artesunate in Sprague Dawley Rats

Purpose of the study: The purpose of this interventional, non-clinical study is to fulfil FDA and EMA Post Marketing Requirements. The study will test for the potential toxic effects/disturbances resulting from Artesunate treatment of Sprague Dawley CD (Crl:CD[SD]) female rats before cohabitation, through mating and to implantation. This study evaluates ICH Harmonised Tripartite Guideline Stages A and B of the reproductive process and should detect effects on the oestrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryos of female rats.