Information to be included with an application for inclusion of a medicine in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion

We propose to include the **fixed-dose** combination of artesunate / mefloquine (Artequin™ Paediatric Stickpacks containing 50 mg artesunate and 125 mg mefloquine each) in the WHO essential drug list as a fixed dose artemisinin-based combination therapy (ACT) for the treatment of uncomplicated P. falciparum malaria in paediatric patients with a body weight of 10 to 20 kg.

The new Artequin™ Paediatric oral formulation is one of the very few fixed-dose ACT's specifically developed for small children (i.e., body weight of 10 to 20 kg, approximately corresponding to an age between 1 and 6 years). It is a mango flavoured, taste-masked preparation of pellets of 50 mg artesunate and 125 mg mefloquine conditioned in one single Stickpack (3 Stickpacks for a 3-day treatment of acute uncomplicated P. falciparum malaria).The once daily treatment with one stickpack containing pellets allows a simple and highly effective treatment, contributing to a better patient compliance.

The dosage of Artequin Paediatric follows the official current WHO recommendations, i.e., to combine high mefloquine dose (i.e., 25 mg/kg total dose over 3 days) with artesunate (4 mg/kg once a day for 3 days). With the combination of a total dose over 3 days of 150 mg artesunate and 375 mg mefloquine, Artequin Paediatric is a dose-linear line extension of the already introduced Co-Blister formulations of Artequin 300/750 for children (body weight range of >20 to 40 kg) and Artequin 600/1500 for adults (body weight > 40 kg).

2. Name of the focal point in WHO submitting the application

Not applicable

3. Name of the organization(s) consulted and/or supporting the application

The artesunate / mefloquine combination (Artequin™) is one of the WHO recommended ACT's.

Prof. Christoph Hatz, of the Swiss Tropical Institute (STI) in Basel / Switzerland has been consulted for the clinical development of the Artequin™ Concept and supports this application.

Artequin™ Paediatric is a line-extension of the already existing Artequin™ co-blister oral dosage forms. A complete pharmaceutical/technical, preclinical and clinical documentation on Artequin™ Paediatric has been prepared. This complete documentation has been submitted to WHO pre-qualification team as well as to WHO GMP department.

4. International Nonproprietary Name (INN, generic name) of the medicine

The artesunate / mefloquine stickpack is a fixed dose combination of two antimalarial drugs: Artesunate (INN) and Mefloquine hydrochloride (INN). In the public market the product is known under the brand name Artequin™ Paediatric.

5. Dosage form or strength proposed for inclusion

5.1 Chemical characteristics:

Mefloquine hydrochloride is chemically *(RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2SR)-piperidin-2-yl]methanol hydrochloride*. The white or slightly yellow, crystalline powder is very slightly soluble in water, freely soluble in methanol, and soluble in alcohol. It melts at about 260°C with decomposition and shows polymorphism. The polymorph used by Mepha is of type C.

Artesunate is chemically *(3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3j]-1,2-benzodioxepin-10-ol, hydrogen succinate*. It is a fine, white crystalline powder which is very slightly soluble in water, very soluble in dichloromethane, and freely soluble in ethanol and acetone.
Both active pharmaceutical ingredients are micronised before use.

5.2 The formulation proposed for inclusion:

The dosage form is constituted of pellets and a powder mixture filled in stickpacks. Each stickpack contains 50 mg Artesunate and 125 mg Mefloquine (corresponding to 137 mg Mefloquine hydrochloride) as drug substances.

Artesunate plus Mefloquine is one of the three WHO-recommended ACTs to treat uncomplicated *P. falciparum* malaria.

The Artesunate/ Mefloquine stickpack is an innovative fixed-dose ACT, especially developed for small children (10-20 kg). This fixed-dose combination was developed to ensure that patients take both drugs together in the right dose, with a particular attention paid to paediatric needs:
- no water is needed to apply the pellets
- the dosing scheme is easy and simple: 1 fixed dose daily for 3 days
- the drug is easy to swallow, with a pleasant taste of mango

5.3 Stability of the formulation

Currently, three scale batches of Artesunate 50 mg / Mefloquine 125 mg Stickpacks are subject to a full stability programme including accelerated testing at 40°C / 75% RH.

Based on the stability data obtained over a period of up to 12 months and the supportive date of the development batches a provisional shelf-life of 18 months can be presumed for the preparation Artesunate 50 mg / Mefloquine 125 mg stickpacks when it is stored below 25°C.
Three production scale batches will be subject to a full stability programme.
The stability studies on all mentioned batches will be continued up to the proposed end of shelf-life of 36 months.

6. International availability –sources, if possible manufacturers

6.1 Sources of the active ingredients:

Mefloquine HCl is manufactured by:
CILAG AG
Hochstr. 201
CH-8205
Switzerland

Artesunate is manufactured by
IPCA Laboratories Ltd.
P.O Sejavta
Dist. Ratlam
Pin: 457 002
India

Or alternatively by

Cambrex Profarmaco Landen
Industriepark Roosvelt 2, B6
3400 Landen
Belgium

6.2 Manufacturer of the finished product:

The fixed dose combination of Artesunate/ Mefloquine HCl is manufactured by Mepha Ltd. in its manufacturing plant:
Dornacherstrasse 114
4147 Aesch
Switzerland

The manufacturer is certified as GMP compliant by its local authorities.
A WHO inspection was also carried out from 25 to 27 April 2005 and the manufacturer was compliant with the principles and guidelines of WHO Good Manufacturing Practices.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Artesunate / Mefloquine fixed-dose combination (Artequin™ Paediatric Stickpacks containing 50 mg artesunate and 125 mg mefloquine each) should be listed in the WHO essential drug list within the pharmacotherapeutic group “antimalarial medicines for curative treatment”.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Malaria is the most important of all tropical diseases and despite considerable efforts to eradicate or control the disease, malaria continues to be a major cause of human morbidity and mortality in the tropics, particularly in Africa and South-East Asia. Worldwide prevalence of the disease is estimated to be in the order of 300-500 million clinical cases each year and more than 90% of all malaria cases are in sub-Saharan Africa.

In fact, out of more than 1 million deaths due to malaria in endemic regions each year, more than 80% occur in Africa south of the Sahara and over 75% occur in African children under 5 years infected with *Plasmodium falciparum*. About 1 in 5 (approx. 18%) of all childhood deaths in African is due to malaria resulting in one child’s death due to malaria every 30 seconds. In addition, an even greater proportion of child deaths is indirectly related to malaria: malaria infections contribute to the development of severe anaemia and make young children more susceptible to severe outcomes of common illnesses such as diarrhoea and respiratory diseases.

Treatment of Plasmodium falciparum malaria in Africa is increasingly difficult. Resistance to cheap efficient antimalarial drugs poses an increasing threat.This is especially worrying in West Africa, where many health services depend on chloroquine as the first-line treatment of uncomplicated malaria, despite chloroquine resistance becoming more common.

WHO, on the advice of international experts, recommends the introduction of combinations of drugs to replace single drugs in the treatment of Plasmodium falciparum malaria. WHO recommends in particular the use of drug combinations containing the peroxidic antimalarial artemisinin (derived from the herb Artemisia annua) and its derivatives such as artesunate, i.e., artemisinin-based combination therapies (ACT), which provide an immediate solution to the problem of drug resistance.
These recommendations led to the selection of two highly potent ACT partner drugs, namely artesunate and mefloquine, as active ingredients of Artequin Co-blister tablets as well as the fixed-dose combination (FDC) of Artequin Paediatric Stickpacks.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

<u>Posology and method of administration:</u>

Patients with a body weight between 10 and 20 kg
A treatment course with Artequin Paediatric comprises 3 stickpacks, each containing 50 mg artesunate and 125 mg mefloquine. One stickpack is to be taken once daily for 3 consecutive days.

The first stickpack is given at the time of initial diagnosis, followed by a second stickpack 24 hours thereafter and a third (last) stickpack 48 hours after the initial one.
If any Artequin Paediatric daily dose (1 stickpack) is missed, the patient should be advised to take the missed dose as soon as it is realised that it has been forgotten. Then the next dose should be taken after a further 24 hour interval.
Patients who vomit within 1 hour after administration of any Artequin Paediatric daily dose (1 stickpack) should be given a replacement (full) dose. In this case, the prescription of another Artequin Paediatric box should be considered. Parts of this new box may be used to ensure that the patient will complete a 3-day full treatment course with Artequin Paediatric.
The combination of artesunate and mefloquine can also be used to treat malaria caused by mixed Plasmodium pathogens. Following treatment with Artequin of malaria caused by a mixed infection with P. vivax, relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered to eliminate hepatic forms of the parasite.

Patients with more than 20 kg body weight
For these patients higher Artequin dosage regimens are recommended depending on the body weight.

Patients with less than 10 kg body weight
Artequin Paediatric is not recommended for use in patients who have less than 10 kg body weight.

Method of administration
Just before administration, the Artequin Paediatric stickpack should be opened (following the pre-printed doted line on the top of the stickpack) and its content (pellets) should be administered directly on to the patient's tongue.
In case of direct mouth administration difficulties, the stickpack content can be put on a spoon and administered with a small amount of liquid.
The mouth should thereafter be rinsed with some liquid, e.g. with milk or water, and remaining pellets swallowed. Patients should be encouraged to resume normal food intake as soon as food can be tolerated.

For further information please refer to the Summary of the Product Characteristics enclosed in section 15.

10. Summary of comparative effectiveness in a variety of clinical settings:

The pharmacokinetic and clinical efficacy of the Artesunate / mefloquine combination is fully presented in the registration file Artequin Paediatric which has been submitted to WHO pre-qualification team as well as to WHO GMP department.

An identification of the clinical evidence and a summary of available data are presented in details in section 2.5.2 Overview of Biopharmaceutics and section 2.5.4 Overview of Efficacy of the **Artequin Paediatric Stickpack Clinical Overview Document** (module 2.5 of the registration file) as well as in the **Artequin Paediatric Stickpack Clinical Summary Document** (module 2.7 of the registration file).

Both documents are attached to this application.

Conclusions on efficacy of the artesunate/mefloquine combination:

A considerable number of clinical studies have evaluated and confirmed the excellent efficacy of the artesunate-mefloquine combination regimen in uncomplicated malaria. These promising findings led Mepha to the development of the Artequin concept with pre-packed combination-blisters of the already marketed artesunate and mefloquine tablets for one course of a three-day therapy.

The two randomized, double blind, parallel group, comparative, phase III studies investigating three different solid oral dosage strengths of Artequin (600/1500, 600/750 and 300/750) have proven in adults and children with uncomplicated malaria the high efficacy and adequate tolerability of this combination product.

The series of post-marketing Artequin studies conducted in different malaria endemic regions of Africa confirm the high efficacy of the Artequin therapy concept also in an extended therapeutic range for

children below a body-weight of 30 kg and for adults of more than 55 kg. The overall experience out of these Artequin studies strengthened the decision to continue the clinical development plan of Artequin with the final goal to provide a fixed-dose combination of artesunate/mefloquine based on a pellet formulation for both active substances, and to further extend the dose range to small children not able to swallow tablets.

Several pharmacokinetic and in-vitro investigations build the basis for a successful dose-linear downscaling of the high mefloquine dose formulation of Artequin Co-blister to the first real galenical formulation for small children, namely Artequin Paediatric Stickpack. Following findings and conclusions out of these investigations are of importance:

- Bioequivalence demonstrated between the mefloquine tablet formulation of Artequin and the reference product Lariam allows to conclude on similarity between the two formulations regarding efficacy and safety.
- Lack of clinically relevant pharmacological interaction between the two active ingredients artesunate and mefloquine allows to take for reference the huge clinical experience with the single substances in the dose designed for the FDC of Artequin Paediatric Stickpacks (daily doses of artesunate 50 mg and mefloquine 125 mg). As a consequence, PK characteristics of both artesunate and mefloquine are supposed to be basically identical when administered alone or in combination. Therefore, the special clinical properties of the two antimalarials (fast but short acting artesunate – long lasting additive and protective effect of mefloquine) which are important for the ACT concept as used in the FDC Artequin Paediatric, are fully maintained in the combination.
- The proven linear dose dependency and proportionality of the pharmacokinetics of artesunate in the dose range of 50 to 200 mg and the known dose-linearity of mefloquine up to a dose of 1000 mg is an important prerequisite for down-scaling the artesunate/mefloquine combination from the already existing dosage forms of Artequin 600/1500 and 300/750 in dose-linear proportionality to Artequin Paediatric, i.e., to further halve the dose to the total therapeutic dose of 150 mg artesunate and 375 mg mefloquine.
- Similarity between the in-vitro dissolution profiles of the artesunate as well as mefloquine pellets in Artequin Paediatric and of the artesunate and mefloquine tablets in Artequin Co-blister demonstrate pharmaceutical equivalence of the two formulations. As a consequence, similar release of the active ingredients in the gastrointestinal tract, and thus, similar absorption patterns can be expected resulting in similar pharmacokinetic and pharmacodynamic characteristics of both the Artequin Co-blister dosage forms and the FDC of Artequin Paediatric.

Study AM-P 001-2005, carried out on children with acute uncomplicated *P. falciparum* malaria in Gabon provides a formal prove that the galenical dose-linearity realised in the dosage of Artequin Paediatric results in similar PK characteristics in children with a body weight of 10 to 20 kg as reached with the double dose, i.e., with Artequin 300/750 given to children with body-weight >20 to 40 kg. As consequentially expected, the study outcome showed an appropriate efficacy of Artequin Paediatric Stickpacks and Artequin 300/750 co-blisters as measured by 28-day and 14-day cure rates of 100% with rapid parasite and fever clearance, in their respective target population. These high healing rates were in line with those demonstrated in the other clinical studies (all post-marketing phase IV as well as the randomized, comparative phase III studies). Irrespective of the dose administered with regard of the mefloquine partner drug of Artequin, there were never issues regarding the efficacy of the therapy over the whole dose-range investigated.

Acceptability of intake of study medication is of great importance in pediatric patient populations as a prerequisite for compliance. Acceptability in the total paediatric study group kept constant above 80% over all three days of therapy which also demonstrate that no negative experience was linked to the drug administration, neither with tablets from Artequin 300/750 nor with the pellet formulation of Artequin Paediatric.

11. Summary of comparative evidence on safety

The safety of the Artesunate / mefloquine combination is fully presented in the registration file Artequin Paediatric which has been submitted to WHO pre-qualification team as well as to WHO GMP department.

A description of adverse effects/reactions and a summary of available data are presented in details in section 2.5.5 Overview of Safety and section 2.5.6 benefits and Risks conclusions of the **Artequin Paediatric Stickpack Clinical Overview Document** (module 2.5 of the registration file) as well as in the **Artequin Paediatric Stickpack Clinical Summary Document** (module 2.7 of the registration file).

Both documents are attached to this application.

Conclusions on safety of the artesunate/mefloquine combination:

Overall, a reasonable safety profile has been reported in clinical studies with artesunate and mefloquine combination regimens. The relationship to study medication is rarely defined with certainty since similar symptoms as reported also rely to the malaria disease itself. For instance, the most commonly reported adverse effects were gastrointestinal disorders like abdominal pain, nausea, vomiting and diarrhoea, all of which are characteristic of acute malaria. Reported nervous system disorders like headache, dizziness and insomnia are, on the other hand, well known mefloquine-related side effects, and therefore, not unexpected in the combination therapy with artesunate/mefloquine. The likelihood of underreporting of AEs in small children has previously been discussed and should be taken into consideration while discussing incidences of AEs**.**

The safety observations in the set of clinical studies with Artequin were of particular interest, since tolerability of the regimen is a crucial determinant for compliance. The overall safety profile of Artequin was adequate and clinically acceptable irrespective of patient age and reflected the well-known profiles of both drugs when used as monotherapy. The evaluation of the safety data out of the post-marketing Artequin studies with special focus on the paediatric population revealed no dose-dependency of the incidence of AEs within the group of small children with a BW between 10 to 20 kg, i.e., the target population for Artequin Paediatric. Thus, small children apparently tolerate the high dose Artequin therapy (as defined by the mean total mefloquine dose of 25 mg/kg) equally well, as demonstrated by the low incidence of gastrointestinal and neurological/psychiatric symptoms. Neither new clinically significant adverse reactions nor severe AEs have been observed with Artequin in the whole set of post-marketing studies.

The good tolerability of Artequin Paediatric in small children with acute uncomplicated *P falciparum* malaria was confirmed in Study AM-P 001-2005. Most of the observed changes in laboratory tests and vital signs were likely to reflect the recovery from the malarial disease rather than safety problems related to the study treatment. Many reported signs and symptoms were likewise due to intercurrent metazoan parasite infections, a situation not to be neglected in malaria endemic regions. As in the other Artequin studies described before, no severe nor serious Adverse Events related to the study medications have been reported in Study AM-P 001-2005.

The advantageous safety profile of Artequin in the whole paediatric population investigated has to be highlighted considering the fact that both study medications, i.e., Artequin 300/750 and Artequin Paediatric, contain the higher mean total mefloquine dosage of 25 mg/kg as currently recommended by the WHO for both Asia and Africa.

Estimate of total patient exposure to Artequin Paediatric to date and Post-marketing Pharmacovigilance:

Since its first launch in West African countries in May 2006, a total number of 343'000 children with a body weight of 10 to 20 kg have been treated with Artequin Paediatric. This number is based on the number of packs sold, i.e. one pack represents one full treatment.

Continuous overall pharmacovigilance evaluation of the Artequin product range during the post-authorisation period is conducted. A Periodic Safety Update Report (PSUR) on Artequin™ / Artequin™ Paediatric covering the period 2000 to 31 July 2006 including data on worldwide marketing authorization status, exposure data, and adverse drug reaction on the artesunate-mefloquine combination formulations registered by Mepha Ltd and evaluating the benefit-risk profile has been generated and concluded on the following points:

- It was estimated that exposure to the different Artequin™ dosage strengths during the PSUR period corresponded to at least a total of 1'716'600 patients.

- 3 serious cases reports of adverse drug reactions were reported during the period covered by this PSUR, 1 was listed and 2 other one were unlisted but considered not related to the drug intake

- During the PSUR period, there were no regulatory authority's or MAH's actions taken for safety reason.

- It was concluded that the general benefit/risk ratio on Artequin™ / Artequin Paediatric™ showed a positive profile and the registration should be maintained.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1. Range of costs of the proposed medicine

One full treatment with one pack of Artequin Paediatric containing 3 stickpacks is priced for approximatively USD 7.--. This public selling price might be different from country to country, depending on the importation and customs duties as well as margins of wholesalers and pharmacists.

12.2. Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

A direct comparison with other antimalarials for small children is not possible as there are no other comparable drugs available, i.e. fixed-dose ACT's for small children. The comparison with e.g. Co-Artesiane Suspension (artemether+lumefantrine dry powder) shows that in most countries of West Africa, this product is sold at a higher price. The same is true for the private market selling price of Coartem tablets which have to be crushed for the application in small children.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Please be informed that Artesunate/Mefloquine stickpack (i.e Artequin™ Paediatric) is not sold in its country of origin, Switzerland, as malaria is not endemic in this country.

Following endemic countries have granted local Marketing Authorisation: Benin, Burkina Faso, Cameroon, Chad, Congo (Brazzaville), Gabon, Guinea, Ivory Coast, Niger, Nigeria, Senegal and Togo.

Registration procedures are ongoing in a certain number of other African countries: Ethiopia, Kenya, Mali, Mauritius, Sudan, Tanzania and Uganda.

In parallel, on December 22, 2006 Mepha Ltd. submitted the fixed dose combination dossier to the World Health Organisation, as part of the pre-qualification registration program concerning Artemisinin based antimalarial products.
The Dossier is under examination by the WHO assessors.

14. Availability of pharmacopoieal standards (British Pharmacopoeia, International Pharmacopoiea, United States Pharmacopoeia)

The drug substances used in the formulation are Mefloquine hydrochloride and Artesunate which are antimalarial drug substances. Artesunate is described in the International Pharmacopeia and Mefloquine hydrochloride is described in the European Pharmacopeia

15. Proposed (new/adapted) text for the WHO Model Formulary

1. Name of the Medicinal Product

Artequin™ Paediatric

2. Qualitative and Quantitative Composition

Each packing of Artequin Paediatric is composed of:

3 stickpacks containing each 50 mg artesunate and 125 mg mefloquine base (in the form of 137.0 mg mefloquine hydrochloride).

For excipients, see section 6.1.

3. Pharmaceutical Form

Stickpack of pellets and powder

4. Clinical Particulars

4.1 Therapeutic indications

Artequin Paediatric is indicated for the oral treatment of non-complicated P. falciparum malaria occurring in endemic areas, in patients with a body weight between 10 and 20 kg.

Artequin Paediatric can also be used in multi-drug resistant areas or areas where resistance is developing to current therapies for P. falciparum infection.

4.2 Posology and method of administration

Patients with a body weight between 10 and 20 kg

A treatment course with Artequin Paediatric comprises 3 stickpacks, each containing 50 mg artesunate and 125 mg mefloquine. One stickpack is to be taken once daily for 3 consecutive days.

The first stickpack is given at the time of initial diagnosis, followed by a second stickpack 24 hours thereafter and a third (last) stickpack 48 hours after the initial one.

If any Artequin Paediatric daily dose (1 stickpack) is missed, the patient should be advised to take the missed dose as soon as it is realised that it has been forgotten. Then the next dose should be taken after a further 24 hour interval.

Patients who vomit within 1 hour after administration of any Artequin Paediatric daily dose (1 stickpack) should be given a replacement (full) dose. In this case, the prescription of another Artequin Paediatric box should be considered. Parts of this new box may be used to ensure that the patient will complete a 3-day full treatment course with Artequin Paediatric.

The combination of artesunate and mefloquine can also be used to treat malaria caused by mixed Plasmodium pathogens. Following treatment with Artequin of malaria caused by a mixed infection with P. vivax, relapse prophylaxis with an 8-aminoquinoline derivative (e.g. primaquine) should be considered to eliminate hepatic forms of the parasite.

Patients with more than 20 kg body weight

For these patients higher Artequin dosage regimens are recommended depending on the body weight.

Patients with less than 10 kg body weight

Artequin Paediatric is not recommended for use in patients who have less than 10 kg body weight.

Method of administration

Just before administration, the Artequin Paediatric stickpack should be opened (following the pre-printed doted line on the top of the stickpack) and its content (pellets) should be administered directly on to the patient's tongue.

In case of direct mouth administration difficulties, the stickpack content can be put on a spoon and administered with a small amount of liquid.

The mouth should thereafter be rinsed with some liquid, e.g. with milk or water, and remaining pellets swallowed. Patients should be encouraged to resume normal food intake as soon as food can be tolerated.

4.3 Contra-Indications

Artequin Paediatric is contraindicated in patients with a known hypersensitivity to artesunate or mefloquine, to their chemically related compounds like other artemisinin derivatives, quinine, quinidine or chloroquine, or to any other ingredient of the stickpack content. Artequin Paediatric must not be used together with halofantrine.

4.4 Special warnings and special precautions for use

Artequin Paediatric is not recommended for the prophylaxis of malaria.

In epileptics, mefloquine may increase the risk of seizures. In these patients Artequin Paediatric should therefore only be used if absolutely required by the medical condition.

Halofantrine, which is known to cause QT interval prolongation, must not be administered concomitantly with or after a mefloquine-containing antimalarial agent like Artequin, because of the risk of a potentially fatal prolongation of the QT interval.

Incidents of dizziness, disturbed sense of balance or neuropsychiatric reactions have been reported both during use and up to three weeks after the last dose of mefloquine due to its long half-life. Therefore, caution is also advised in patients receiving any dos-age regimen of Artequin when pursuing activities requiring full attention and fine-motor co-ordination for example driving vehicles and operating machinery.

Artequin Paediatric is not recommended for use in patients who have less than 10 kg body weight.

Higher Artequin dosage regimens are recommended for use in patients who have more than 20 kg body weight.

4.5 Interaction with other medicinal products and other forms of interaction

So far, there have been no reports of negative drug interactions with artesunate.

Concomitant administration of mefloquine and related substances (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions. Therefore, halofantrine, which is known to cause QT interval prolonga-tion, must not be administered concomitantly with or after

Artequin for at least 3 weeks. In patients undergoing treatment with anticonvulsives such as valproic acid, carbamazepine, phenobarbital or phenytoin, mefloquine contained in Artequin may lower the plasma concentration of the anticonvulsive, resulting in seizures. In such cases, it may be required to adjust the dosage of the anticonvulsive (see also section 4.4).

4.6 Pregnancy and lactation

Pregnancy category C

Clinical experience with artesunate or mefloquine used as monotherapy has not revealed any embryotoxic or teratogenic effects. However, as experience in pregnant patients is limited, Artequin should not be administered during pregnancy unless the treatment is considered life saving and the expected benefit justifies the potential risk for the foetus.

Mefloquine passes in small quantities into breast milk, the effects of which are, however, unknown. Therefore, decision should be made whether to treat the mother with Artequin, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

As outlined under section 4.4, possible side effects of mefloquine necessitate caution when driving and using machines during and up to three weeks after therapy with a mefloquine containing antimalarial agent like Artequin.

4.8 Undesirable effects

Adverse events experienced by patients taking antimalarial drugs often mirror the symptoms of an acute malaria infection. It may therefore not be possible to distinguish undesirable effects of Artequin Paediatric from the symptoms of the disease.

The most common adverse experiences reported in clinical studies on patients treated with Artequin were:

Gastrointestinal disorders

Common*: abdominal pain, nausea, vomiting and diarrhoea

Nervous system disorders

Common*: headache, dizziness and insomnia

General and metabolism disorders

Common*: asthenia, anorexia and hypokalaemia

* Common: 1 to 10%.

Most of these adverse events were of mild to moderate severity and occurred with a similar frequency, when historically compared to the incidence rate of adverse events observed in patients receiving either drug as monotherapy.

No other significant adverse effects have been observed in patients treated with Artequin. The following most common adverse events have been reported in the literature with the combination of artesunate and mefloquine: headache and allergic reactions including rash and pruritus. In rare cases mild and transient reduction in reticulocytes and neutrophil granulocytes, as well as transient increase in transaminases and total bilirubin have been described. Nevertheless, any other side effects that have been reported with either artesunate or mefloquine used as monotherapy could also occur with Artequin Paediatric.

Undesirable effects also reported with artesunate monotherapy

Clinical laboratory findings occasionally showed mild and transient reduction in reticulocytes and neutrophil granulocytes, especially the young forms, but there were no symptoms or signs of superimposed infections. In rare cases, transient increases in transaminases have been reported.

Other undesirable effects reported with mefloquine monotherapy

The most frequently reported adverse effects are nausea, vomiting, soft stools or diarrhoea and abdominal pain, dizziness or vertigo, disturbed sense of balance as well as neuropsychological adverse effects such as headache, somnolence and sleep disorders (sleeplessness, unusual dreams).

Less frequent adverse effects reported with mefloquine monotherapy

Central and peripheral nervous system: sensory and motor neuropathies (including paresthesia, tremor, ataxia), convulsions, agitation, visual disturbances, tinnitus and vestibular disturbances, anxiety, restlessness, depression, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression as well as psychotic or paranoid reactions. There have been rare reports of suicidal ideations; however, a relationship to the administration of the drug could not be demonstrated.

Cardiovascular system: circulatory disorders (hypotension, hypertension), skin reddening, unconsciousness, chest pain, tachycardia or palpitation, bradycardia, irregular heart-beat, extrasystoles and other transient conduction disturbances.

Skin: skin rash, exanthema, erythema, urticaria, pruritus, oedema, hair loss.

Locomotor system: muscle weakness and muscle cramps, myalgia, arthralgia.

General symptoms: hearing impairment, dyspnoea, asthenia, malaise, fatigue, fever, sweating, chills, dyspepsia and loss of appetite.

Laboratory abnormalities: transient increase of the transaminases, leucopenia or leucocytosis, thrombocytopenia.

Isolated cases of erythema multiforme, Stevens-Johnson syndrome, AV-block and encephalopathy have been reported.

Adverse reactions to mefloquine can occur or last for several weeks after the last dose on account of the long half-life.

Neither in vitro nor in vivo studies suggest evidence of haemolysis in connection with a glucose-6-phosphate dehydrogenase deficiency.

4.9 Overdose

So far, no cases of overdose have been reported with artesunate. Overdosage with mefloquine may lead to increased occurrence of the mefloquine-related adverse effects.

Recommended therapy in case of Artequin Paediatric overdosage consists of vomiting or gastric lavage and careful monitoring of the cardiac function (if possible by ECG) and of the neuropsychiatric status (for at least 24 hours).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial

ATC code: Artesunate: PO1B E03

Mefloquine: PO1B C02

Artequin Paediatric is a fixed-dose combination of two antimalarial drugs, artesunate and mefloquine. Artesunate is a water-soluble hemisuccinate ester of artemisinin, the main antimalarial substance isolated from Artemisia annua and mefloquine is an antimalarial agent of the 4-quinoline methanol group.

Both active ingredients are schizonticidal and destroy the erythrocytic asexual forms of the causative agents of malaria in humans (Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale). Artequin is usually also effective against ma-laria pathogens that have developed resistance to either agent used alone and to other antimalarial agents such as chloroquine, proguanil, pyrimethamine as well as pyrimethamine-sulfadoxine combinations.

A three-day treatment course with a combination of artesunate and mefloquine was shown to induce faster symptomatic response with shorter parasite clearance times than mefloquine alone, and less recrudescences as compared to artesunate monotherapy when used for less than 5 days.

In randomised, double blind, parallel group, comparative, multicenter studies in more than 300 patients with uncomplicated P. falciparum malaria, Artequin (free combination) showed a 100 % cure rate at day 28, and overall mean fever and parasite clearance times of less than 48 hours.

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics of the artesunate and mefloquine combination have been investigated in various clinical studies. There was no evidence of a clinically significant interaction between the two antimalarial agents.

Absorption

Artesunate

Following oral administration, artesunate is quickly absorbed and reaches a maximum plasma concentration (Cmax) on average between 0.5 and 1 hour.

Mefloquine

Following single oral administration of mefloquine, a maximum plasma concentration is reached within 6 to 24 hours (mean 17 hours). At a dose of 1000 mg of mefloquine, plasma concentrations (Cmax) of approximately 1000 µg/l can be measured. The presence of food in the stomach increases the rate and extent of absorption and leads to an increase in bioavailability of approximately 40%.

Distribution

Artesunate

The concentration of DHA (dihydroartemisinin, the bioactive metabolite of artesunate) in P. falciparum-infected erythrocytes in vitro was found to be 300-fold the plasma concentration (compared to less than 2-fold for uninfected erythrocytes). Artesunate and DHA bind modestly to human plasma protein. The degree was found to be about 59% for artesunate and 43% for DHA.

Mefloquine

Depending on the parasitaemic state and the duration of the infection, the concentration of mefloquine in erythrocytes is almost two to four times that of the plasma concentration. The volume of distribution is between 16 and 25 l/kg. More than 98% of the active ingredient is bound to plasma proteins.

Mefloquine crosses the placental barrier and reaches breast milk in apparently minimal amounts.

Metabolism

Artesunate

In vivo, artesunate is hydrolysed rapidly, probably by blood esterases and the hepatic cytochrome P450 system, to dihydroartemisinin (DHA), which is also highly effective against malaria.

Mefloquine

Several metabolites of mefloquine have been identified. The major metabolite is the corresponding quinoline carboxylic acid, which is inactive against P. falciparum.

Elimination

Artesunate

The mean elimination half-life of artesunate is approximately 0.5 hours. The active metabolite dihydroartemisinin (DHA) has a mean elimination half-life of 0.75 hours and is eliminated slower than the parent compound. DHA is cleared predominantly by hepatic biotransformation to pharmacologically inactive metabolites.

Mefloquine

The mean elimination half-life of mefloquine is 21 days (15-33 days). Total clearance, which is essentially hepatic, is approximately 30 ml/min. There is evidence that mefloquine is eliminated mainly via bile and faeces. In healthy volunteers, elimination of un-changed mefloquine and its major metabolite in urine was 9% and 4%, respectively, of the administered dose. It was not possible to determine the concentrations of other metabolites in the urine.

Kinetics in special clinical situations

There have been no specific pharmacokinetic studies for mefloquine and artesunate in patients suffering from renal insufficiency, however, only a small fraction of these active substances is eliminated via the kidneys. It should be noted that mefloquine and its principal metabolite are not removed to an appreciable extent by haemodialysis. Accordingly, no dose adjustment is necessary for Artequin in patients with impaired renal function.

It has been shown that hepatic insufficiency has no effect on the bioavailability and clearance of oral artemisinin. However, no specific data is available on the use of artesunate in this patient population. In addition, the elimination of mefloquine in such patients may be delayed, which leads to higher plasma concentrations. Therefore caution is advised in patients with hepatic insufficiency receiving Artequin.

The pharmacokinetics of mefloquine may be modified in acute malaria.

Pharmacokinetic differences regarding mefloquine have been observed between various ethnic populations. In practice however, these are of minor importance compared to the immune status of the host and the sensitivity of the parasite.

5.3 Preclinical safety data

Available preclinical data on artesunate and mefloquine did not reveal any special hazard for humans.

6. Pharmaceutical Particulars

6.1 List of excipients

Artesunate and mefloquine pellets:

Microcrystalline cellulose; lactose monohydrate; povidone; sodium starch glycolate (type A); basic butylated methacrylate copolymer; talc; titanium dioxide (E171); silica, colloidal hydrated

Powder (outer phase):

Xylitol; carmellose sodium; sodium cyclamate; saccharin sodium; talc; mango aroma

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

18 months

6.4 Special precautions for storage

Do not store above 25°C.

Keep out of the reach and sight of children.

Do not use this drug after the expiry date stated “EXP” on the packaging.

6.5 Nature and contents of container

Artequin Paediatric is composed of pellets and powder filled in stickpacks (consisting of layers of the following materials, from the inner to the outer layer: polyethylene film, soft aluminium foil, polyethylene foil and paper).

6.6 Instruction for use/handling

No special requirements.

7. Marketing Authorization Holder

8. Marketing Authorization Number(s)

9. Date of first authorization/Renewal of authorization

10. Date of (partial) revision of the text
December 2005