SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets*

Artesunate 25mg + Mefloquine (as hydrochloride) 50mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla tablet contains 25 mg of artesunate and 50 mg of mefloquine (as hydrochloride)

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Blue, round, smooth, biconvex, film-coated tablets.
The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets are indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria, in the setting of either *P. falciparum* mono-infection or mixed infections in children and infants of 5 kg and above.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets.

Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and public health authorities' guidelines (see also sections 4.4 and 5.1).

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

4.2 Posology and Method of Administration

Posology

The recommended daily dose of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets is a best approximation of the target dose for each drug:
4 mg/kg/d for artesunate and 8 mg/kg/d for mefloquine, corresponding to total doses over 3 days of 12 mg/kg and 24 mg/kg, respectively.

Where accurate weighing scales are available, dosing should be based on weight. If these scales are not available dosing of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets can be based on age categories as shown in the table below. The approximate corresponding weights for these age categories are also shown. In patients at the extremes of weight for the corresponding age (such as in cases of malnutrition or obesity), the dose should be adjusted according to the weight of the patient.

Recommended Dosage for Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets

Weight (kg)	Age	Recommended Dose
5 - < 9	6 - <12 months	**One** Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) CiplaTablet 25 / 50 mg daily for 3 days
9 - < 18	1 - <7 years	**Two** Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets 25 / 50 mg daily for 3 days

For patients weighing 18 kg or more another formulation containing a higher amount of artesunate and mefloquine is available.

If a full treatment course does not lead to improvement within 48 to 72 hours the patient should be reevaluated.

If vomiting occurs within 30 minutes of drug administration, the full daily dose of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets should be repeated. If vomiting occurs more than 30 minutes after dosing, half the recommended daily dose of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets should be given. If the second dose is vomited, alternative antimalarial therapy should be instituted.

If a dose is missed it should be given as soon as it is noted. The next dose should be given after the prescribed interval. The patient should not be given a double dose to make up for a forgotten tablet. The patient's caregiver should make sure to give all three doses of this regimen.

Method of administration

For oral use.

Tablets should be swallowed whole with or without food.

For patients who are unable to swallow tablets, the tablet(s) should be placed on a teaspoon containing clean water and allowed to disintegrate before oral administration. Then the teaspoon should be refilled with water and this liquid should be administered to the child.

Special Populations

Elderly
No adjustment of the adult dosage is recommended for elderly patients.

Paediatric Population
Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets is not recommended for treatment in infants weighing less than 5 kg and/or less than 6 months old.

Renal impairment

There is no evidence that dose adjustment is necessary for patients with renal insufficiency. However, since clinical evidence in such patients is limited, caution should be exercised when using Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets in patients with impaired renal function.

Hepatic Impairment

No adjustment of the dosage is recommended for adult patients with mild to moderate liver impairment. However, in patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions. Caution should be exercised when using Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets in patients with impaired hepatic function.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Known hypersensitivity to quinine, quinidine or any artemisinin
- The recovery period from severe malaria, as mefloquine has been shown to increase the risk of convulsions
- Concurrent or recent halofantrine therapy, due to the increased risk of prolongation of the QTc interval
- Concurrent or recent ketoconazole therapy, due to the increased risk of prolongation of the QTc interval

4.4 Special Warnings and Precautions for Use

Malaria may return despite the use of an effective antimalarial treatment and a good initial clinical response. This can occur if the patient has a late treatment failure (i.e. after an initial reduction in parasite counts they increase again due to failure to achieve complete parasite clearance) or if patients who remain in the malaria endemic region become reinfected. If there is a reappearance of clinical symptoms and signs of malaria, the patient should be immediately evaluated and, if clinically indicated, effective antimalarial treatment should be prescribed. Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets should not be used within two months of a therapeutic dose of mefloquine because of the increased risk of mefloquine-induced neuropsychiatric side effects. Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets have not been evaluated for the treatment of complicated malaria and is therefore not recommended.

There is insufficient evidence for the use of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets in the treatment of malaria due to *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* or *Plasmodium knowlesi.* It is therefore not recommended.

There is insufficient evidence to support the use of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets for prevention of malaria.

Caution should be exercised in:

- Patients with underlying cardiac conduction defects or known cardiac arrhythmias:
  In rare cases, treatment and prophylaxis with mefloquine have been associated with clinically significant adverse events related to cardiac conduction.
- Patients with a history of seizures.
- Patients with severe liver impairment, as mefloquine undergoes hepatic metabolism.

- Patients with thalassaemia, sickle cell anaemia or G6PD-deficiency. No studies have been done in persons with these conditions.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No drug-drug interaction studies have been conducted with the fixed dose combination of artesunate and mefloquine.

Antimalarials

Halofantrine may cause fatal prolongation of the QTc. This has occurred when halofantrine was used with or without prior administration of mefloquine. Therefore, Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets must not be given together or within 21 days after therapy with halofantrine.

Co-administration of mefloquine and quinine produced a modest increase in QTc in patients and volunteers that correlated only with quinine concentrations. There has been extensive experience with the use of a quinine loading dose (20 mg salt/kg) for treating severe falciparum malaria in patients treated earlier with mefloquine with no deleterious cardiac effects. In addition, a study in malaria patients did not find a significant cardiac interaction between the quinine (10 mg salt/kg) dose and oral mefloquine (15 mg/kg) given together.

Quinidine and chloroquine have been associated with prolongation of the QTc interval. Although there are no interaction data with mefloquine for either drug, an increase in the QTc interval is theoretically possible.

Concurrent use of mefloquine with chloroquine or quinine may increase the risk of convulsions.

Cardiac Drugs

A number of cardiac drugs (e.g. quinidine, amiodarone, sotalol, disopyramide) are known to prolong the QTc interval. Therefore, caution is advised when giving Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets with these drugs, as this could increase the risk of QTc prolongation.

Treatment of malaria results in a slowing of the heart rate because of fever resolution. This effect may be exacerbated in patients who are already taking drugs that reduce the heart rate e.g. digoxin, β-blockers, verapamil, diltiazem, or ivabradine (see section 4.8).

Non Cardiac Drugs Producing QTc Prolongation

Drugs associated with QTc prolongation include tricyclic antidepressants, phenothiazines, haloperidol, pimozide, terfenadine, astemizole, ketoconazole, moxifloxacin, cisapride, and metoclopramide. Therefore, caution is advised when giving Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets with these drugs, as this could increase the risk of QTc prolongation.

Antimicrobial Agents / Ketoconazole

Mefloquine concentrations are increased by the co-administration with ampicillin and tetracycline. Mefloquine concentrations are reduced with concomitant use with rifampicin.

Ketoconazole, an inhibitor of CYP3A4, results in increased mefloquine concentrations.

There has been a report of convulsions in three patients treated with mefloquine combined with the quinolones ciprofloxacin, ofloxacin or sparfloxacin.

As noted above, moxifloxacin and ketoconazole are known to induce QTc prolongation in both clinical and preclinical models. Therefore, caution is advised when giving Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets with either drug because of the risk of a prolongation of the QTc interval.

Anticonvulsants

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets should not be given to epileptic patients, as mefloquine reduces the plasma levels of anticonvulsants e.g. carbamazepine, phenobarbital, phenytoin, valproic acid.

However, if no other choice is available, dose adjustment of anti-seizure medication may be necessary during treatment with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets.

Anticoagulants

There are reports of serious bleeding in patients co-administered mefloquine and coumadin. Close monitoring of coagulation parameters is advised. Dose adjustment of oral anticoagulants may be necessary.

Metoclopramide

The concurrent use of metoclopramide with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets may increase the plasma concentrations of mefloquine.

Antiretrovirals

Coadministration of mefloquine and ritonavir (200 mg) decreased ritonavir AUC (31%) and Cmax (36%). Ritonavir did not affect the pharmacokinetics of mefloquine. Clinical consequences are not expected.

Food

There are no food interaction data with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets. Data in *P. falciparum*-infected patients treated with mefloquine and artesunate given as loose tablets did not indicate any consistent effect of food on mefloquine AUC.

4.6 Pregnancy and Lactation

Pregnancy

Artesunate + mefloquine may be used in the second and third trimester of pregnancy. In the first trimester artesunate + mefloquine should be used only if this is the only treatment immediately available or if first-line therapy with quinine plus clindamycin has failed.

Lactation

Mefloquine is secreted into breast milk. Lactating women should receive the recommended antimalarial treatment (including artesunate+mefloquine).

4.7 Effect on Ability to Drive and Use Machines

Mefloquine can cause dizziness and severe vertigo. Patients who experience such side-effects during or after treatment with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets should not drive, operate machinery or perform tasks that require a high degree of manual and/or psychomotor dexterity for at least 3 weeks following use of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets.

4.8 Undesirable Effects

The safety profile of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla tablets is based on a Phase III trial in Thailand conducted in 500 adults and children with uncomplicated *falciparum* malaria, including 251 patients treated with the fixed dose combination and 249 patients in the comparator group treated with a standard 3-day regimen of artesunate and mefloquine, given as separate tablets.

The most frequent adverse events were headache, dizziness, vomiting, nausea, fatigue, pyrexia, arthralgias, myalgias, anorexia, sleep disorders, and palpitations.

Adverse events considered at least possibly related to artesunate and mefloquine are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare and not known (cannot be estimated from the available data).

Cardiac disorders
Very common: Palpitations

Ear and labyrinth disorders
Common: Hearing impaired

Eye disorders
Uncommon: Blurred vision or other visual disturbance

Gastrointestinal disorders
Very common: Vomiting
Common: Nausea, abdominal pain, diarrhoea

General disorders and administration site conditions
Common: Fatigue

Hepatobiliary disorders
Common: Hyperbilirubinaemia
Uncommon: Hepatitis

Infections and infestations
Common: Recrudescence of malaria

Metabolism and nutrition disorders
Common: Anorexia

Musculoskeletal and connective tissue disorders
Common: Myalgia, arthralgia

Nervous system disorders
Very common: Dizziness
Common: Headache

Psychiatric disorders
Very common: Sleep disorder
Uncommon: Hallucination (visual)

Skin and subcutaneous tissue disorders
Uncommon: Pruritus

In the medical literature, other adverse events which have been reported to occur with artesunate, mefloquine, or combinations of the two include anxiety, abnormal dreams, weakness, urticaria, hypersensitivity (allergic) reactions and skin rashes (including erythematous maculapapular rash, erythema multiforme, and Stevens-Johnson syndrome), rigors, tremor, confusion, and numbness. Serious psychiatric adverse events (seizure, depressive syndrome, acute psychosis) and acute intravascular haemolysis with haemoglobinuria have been reported rarely. There have also been reports of mild electrocardiogram (ECG) changes (QTc and PR increases), atrial extrasystoles,

nonspecific T-wave changes, and bradycardia, as well as elevations of transaminases. Their frequencies cannot be estimated from the available data.

4.9 Overdose

Symptoms

In the event of an overdose the symptoms described in Section 4.8 may be more pronounced: cardiac, hepatic and neurological symptoms have been reported.

Treatment

Patients should be monitored by ECG and observed for neuropsychiatric symptoms for at least 24 hours. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Supportive care should be given as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC-Code: Artemisinin and derivatives, combinations (P01BF02)

Artesunate

Artesunate, an artemisinin derivative, and its principal metabolite dihydroartemisinin (DHA) are toxic to malaria parasites at nanomolar concentrations. There is enhanced uptake of the drug by red blood cells infected with parasites, which is rapid and saturable. It is active against all Plasmodium species. It has broad activity against asexual parasites, killing all stages from young rings to schizonts. In *P. falciparum* malaria, artemisinin also kills the gametocytes—including the stage 4 gametocytes.

The peroxide moiety in artemisinin reacts in the presence of haeme. A primary radical alkylates haeme via an intramolecular process to produce covalent haeme-drug adducts. The accumulation of nonpolymerizable redox-active haeme derivatives, a consequence of haeme alkylation, is thought to be toxic for the parasite. The alkylation of haeme by artemisinin has been demonstrated in malariainfected mice, indicating that haeme is acting as the trigger and target of artemisinin.

Mefloquine

Mefloquine is an antimalarial agent with highly active schizontocide activity but is not gametocidal. It is active against chloroquine-resistant *P. falciparum*. The exact mechanism of action of mefloquine is unclear but it is has a high affinity for erythrocyte membranes.

Clinical efficacy of artesunate/mefloquine

The efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets will depend on the drug sensitivities of the local malaria parasites. Resistance has been evidenced by a decline in cure rates of artesunate plus mefloquine given as separate tablets in Western Cambodia and a slowing of parasite clearance in North-Western Thailand.

An open-label clinical study in 500 patients (adults and children) was conducted in North-Western Thailand. Patients treated with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets experienced a Day 63 PCR-corrected cure rate of 91.9% (95% CI 88.2, 95.6), while those treated with the standard loose tablet regimen of artesunate and mefloquine displayed a Day 63 PCR-corrected cure rate of 89.2% (95% CI 85.0, 93.4; Kaplan-Meier analysis, log-rank test for significance).

In an additional, randomized open-label study in 50 adult patients with acute, uncomplicated

P. falciparum malaria conducted in Thailand, 22/24 patients (91.7%) patients treated with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets had parasitological cure at day 28, compared to 24/24 (100%) patients administered artesunate and mefloquine as separate tablets.

An open-label, single-arm study with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets in 77 adult patients with acute, uncomplicated *P. falciparum* malaria conducted in India reported 63-day parasitological cure rates of 100%.

5.2 Pharmacokinetic Properties

Artesunate

According to published data, orally administered artesunate is rapidly hydrolyzed to DHA, primarily by plasma or tissue choline esterases. Due to the rapid conversion, artesunate is often considered as pro-drug of DHA. Following oral administration of artesunate, the ratio of AUC for DHA to AUC for artesunate can be as high as 10:1. Artesunate Cmax concentrations are achieved within 1 hour, and it is eliminated with a half-life of 20 to 45 minutes. Plasma protein binding of artesunate and DHA is moderate (62 to 93%) and albumin is the principal binding protein for DHA in human plasma. The metabolic pathways for DHA was studied in humans by analyzing metabolites in urine collected from patients who had received intravenous AS and metabolites produced by human liver microsomes. It was shown that DHA is metabolized by UGT1A9 and UGT2B7, but not UGT1A1 and UGT1A6. The major metabolite identified was α-DHA-β-glucuronide. AS and DHA undergo extensive first-pass metabolism with very high extraction ratio. For drugs with high extraction ratio, clearance approaches blood flow and is therefore perfusion rate limited. No urinary excretion data are available for humans.

Mefloquine

Mefloquine is absorbed from the gastrointestinal tract and is widely and rapidly distributed throughout the body. The mean times to maximum concentrations range from 6 to 24 hours in healthy volunteers. Plasma levels are higher in patients with malaria than in healthy volunteers. Mefloquine is 98% bound to plasma proteins and is metabolised in the liver by cytochrome P450 isoenzymes to inactive 4-carboxylic acid metabolite, and several other metabolites. Mefloquine has a long half-life of 14- 28 days. Excretion is mainly in the faeces and bile.

5.3 Preclinical Safety Data

Artesunate and mefloquine have been extensively and safely used for many years for the treatment of malaria at doses similar to those used in Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets.

Artemisinin derivatives, of which artesunate is one, have been associated with neurotoxicity following prolonged exposure to very high doses in animals. To date, there is no convincing clinical evidence of neurotoxicity in treated patients. Furthermore, the potential for neurotoxicity in man is highly unlikely given the rapid clearance of artesunate and short exposure (3 days of treatment). Artemisinins are also known to be embryotoxic and artesunate has been shown to cause increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats and rabbits.

In rats and mice, mefloquine has been shown to cross the placenta and is teratogenic in early gestation. Mefloquine is also secreted into breast milk (See Section 4.6).

In vitro, mefloquine blocks preferentially the slow (I_{Ks}) component of the delayed rectifier potassium (K^+) channel in cardiac muscle and, therefore theoretically has the potential to exacerbate the QTc prolongation produced by other drugs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet: Croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

Film coat: Indigo carmine aluminium lake (FD & C Blue #2), hypromellose, macrogol, polysorbate 80 and titanium dioxide.

6.2 Incompatibilities

None.

6.3 Shelf-Life

36 months

6.4 Special Precautions for Storage

Do not store above 30°C

6.5 Nature and Contents of Container

Primary packing: Aluminium-aluminium blister strip with 3 tablets.

Secondary packing**:** Carton having one strip of 3 tablets and carton having 2 strips of 3 tablets.

6.6 Instructions for use and handling and disposal

Not applicable

7. SUPPLIER

Cipla Ltd
Mumbai Central
Mumbai 400008
Maharashtra, India
Phone: (9122)23082891 Fax:
(9122) 23070013
Email: exports@cipla.com

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

MA078

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF THE PREQUALIFICATION

12 September 2012

10. DATE OF REVISION OF THE TEXT

December 2012. Section 6 updated in January 2016. Section 4.2 updated in May 2017.

References

General:

WHO Guidelines for the treatment of malaria -- 2nd edition, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf WHO Update on Artemisinin Resistance September 2011: http://www.who.int/malaria/diagnosis_treatment/resistance/updateartemsininresistancesept2011/en/index.html
Artesunate 50 mg tablets SmPC, Guilin, China: available at (Nov 2012):

http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA044part4v2.pdf
Lariam (mefloquine) SmPC, September 13,2012, Roche Products Limited
http://www.medicines.org.uk/emc/medicine/1701

Drug Interactions:

Karbwang J., Effect of ampicillin on mefloquine pharmacokinetics in Thai males, Eur J Clin Pharmacol 1991, 40(6):631-33.

Karbwang J., Effect of tetracycline on mefloquine pharmacokinetics in Thai males, Eur J Clin Pharmacol 1992, 43(5):567-69.

Mangalvedhekar SS. et al, Convulsions in non-epileptics due to mefloquine-fluroquinolone co-administration. Nat Med J India 2000, Jan-Feb 13(1):47.

Loefler I., Mefloquine and anticoagulant interaction, J Travel Med 2003 May-June 10(3):194-95.

Na Bangchang K., The effect of metoclpramide on mefloquine pharmacokinetics. Br J Clin Pharmacol 1991 Nov;32(5):640-41.

University of Liverpool, UK, HIV Drug Interactions Website www.hiv-druginteractions.org

Pharmacodynamics/Clinical:

Meunier B. et al. Heme as trigger and target for trioxane-containing antimalarial drugs.
Acc Chem Res. 2010 Nov 16;43(11):1444-51. Epub 2010 Aug 30.
http://www.ncbi.nlm.nih.gov/pubmed/20804120

Ashley EA. et al, An open label randomized comparison of mefloquine–artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. Trop Med Int Health. 2006 Nov;11(11):1653-60.
(http://www.ncbi.nlm.nih.gov/pubmed?term=open%20label%20randomized%20comparison%20new%20coformulated%20)

Smithhuis F. et al, Effectiveness of Five Artemisinin Combination Regimens with or without Primaquine in Uncomplicated Falciparum malaria: an Open-label Randomised Trial
Lancet Infect Dis. 2010 Oct;10(10):673-81. Epub 2010 Sep 9. http://www.ncbi.nlm.nih.gov/pubmed/20832366

Pharmacokinetics:

Morris CA. et al, Review of the clinical pharmacokinetics of artesunate and its active metabolite dihydroartemisinin following intravenous, intramuscular, oral or rectal administration. Malaria J. 2011; 10: 263. Published online 2011 September 13. doi: 10.1186/1475-2875-10-263
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3180444/ For artesunate:
European Public Assessment Report "Pyramax" (Article 58 procedure):
http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000344.jsp&mid= (as checked on 09 Dec 2012)