药品名称		注射用青蒿琥酯
包材编号		4.6.04.23.024.01.04
说明书	尺寸	520*185mm
	材质	70g书写纸
	备注	3联国内，科麟专用
	修改内容	尺寸修改

包装设计稿 生效日期：	分发部门	彩色稿： QA、QC、科麟 复印稿： 车间、采购部、 生产部、计划部、 物流部
科麟内部审核		
设计：周文会 审核： 批准：		
南药QA审核		
审核： 批准：		

色标：

CMYK:0/0/0/100

核准日期：2007年04月30日
修改日期：2010年07月29日
2012年09月15日
2013年11月18日
2014年09月02日
2015年02月12日
2016年07月15日
2017年07月10日

注射用青蒿琥酯说明书

请仔细阅读说明书并在医师指导下使用

【药品名称】

通用名称：注射用青蒿琥酯

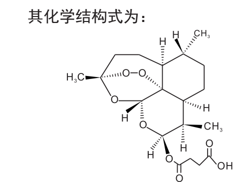
商品名称：Artesun®

英文名称：Artesunate for injection

汉语拼音：Zhusheyong Qinghaohuzhi

【成份】本品主要成份为青蒿琥酯，化学名称为：二氢青蒿素-10α-丁二酸单酯。

其化学结构式为：



分子式：C19H28O8　　分子量：384.42　　无辅料

【性状】本品为白色结晶性粉末。

溶剂（碳酸氢钠注射液）为澄明、无色液体。

溶剂（氯化钠注射液）为澄明、无色液体。

【适应症】适用于脑型疟及各种危重疟疾的治疗。

【规格】

1）60mg

每瓶含青蒿琥酯60mg。

每安瓿溶剂含碳酸氢钠50mg/ml为1ml。

每安瓿溶剂含氯化钠9mg/ml为5ml。

2）120mg

每瓶含青蒿琥酯120mg。

每安瓿溶剂含碳酸氢钠50mg/ml为2ml。

每安瓿溶剂含氯化钠9mg/ml为10ml。

【用法用量】

给药方法

本品可以肌肉注射或静脉注射。本品不得静脉滴注。

本品使用前必须用专用的5%碳酸氢钠溶液溶解，再用5%葡萄糖注射液或0.9%氯化钠注射液稀释，制得一定浓度的注射用溶液后方可使用。

本品肌肉注射时，按所需药量吸取药液，进行肌肉注射。通常大腿前部是首选的注射部位。如果肌注溶液的总量较大，可以采取在几个部位分量注射，例如大腿两侧。

本品静脉注射时，按所需药量吸取药液，缓慢注射1～2分钟以上。

需要特别强调的是，由于缺少研究数据，本品在静脉/肌肉给药时不得与其他药物混用。

剂量及给药方案

成人：

青蒿琥酯每次剂量按成人120mg（2.4mg/kg），分别于第0、12和24小时注射，然后一日一次，直至病人可以口服药物。

使用注射用青蒿琥酯最少需要24小时（3次），病人能够口服治疗时，转为口服复方抗疟药以完成抗疟联合疗法的治疗过程。口服给药按照该复方治疗疟疾的方案进行。

儿童：

儿童每次剂量按照体重确定，推荐的剂量见下表。根据需要可以继续按同等剂量每日给药一次，直至第7天。或病人病情缓解并能口服给药后，转为口服复方抗疟药以完成抗疟联合疗法的治疗过程。口服给药按照该复方治疗疟疾的方案进行。

注射用青蒿琥酯儿童给药剂量（mg）

年龄组（岁）	第一天		第二天
	0小时	12小时	24小时
≥16	120	120	120
11~	90	90	90
7~	60	60	60
＜7	2.4/kg	2.4/kg	2.4/kg

配制：

静脉注射用溶液：

溶解60mg规格产品时，用注射器从安瓿瓶中抽取5%碳酸氢钠溶液1ml，将其注入装有60mg青蒿琥酯粉剂的小瓶中，反复振摇几分钟直至完全溶解澄清后再进行稀释。稀释方法为在溶解后的溶液中再加入5%葡萄糖注射液或0.9%氯化钠注射液5ml，制得6ml青蒿琥酯静脉注射用溶液，每ml该溶液含青蒿琥酯10mg，反复振摇至完全溶解澄清后方可使用。如配制过程中出现浑浊或沉淀物不可使用。

溶解120mg规格产品时，用注射器从安瓿瓶中抽取5%碳酸氢钠溶液2ml，将其注入装有120mg青蒿琥酯粉剂的小瓶中，反复振摇几分钟直至完全溶解澄清后再进行稀释。稀释方法为在溶解后的溶液中再加入5%葡萄糖注射液或0.9%氯化钠注射液10ml，制得12ml青蒿琥酯静脉注射用溶液，每ml该溶液含青蒿琥酯10mg，反复振摇至完全溶解澄清后方可使用。如配制过程中出现浑浊或沉淀物不可使用。

肌肉注射用溶液：

溶解60mg规格产品时，用注射器从安瓿瓶中抽取5%碳酸氢钠溶液1ml，将其注入装有60mg青蒿琥酯粉剂的小瓶中，反复振摇几分钟直至完全溶解澄清后再进行稀释。稀释方法为在溶解后的溶液中再加入5%葡萄糖注射液或0.9%氯化钠注射液2ml，制得3ml青蒿琥酯肌肉注射用溶液，每ml该溶液含青蒿琥酯20mg，反复振摇至完全溶解澄清后方可使用。如配制过程中出现浑浊或沉淀物不可使用。

溶解120mg规格产品时，用注射器从安瓿瓶中抽取5%碳酸氢钠溶液2ml，将其注入装有120mg青蒿琥酯粉剂的小瓶中，反复振摇几分钟直至完全溶解澄清后再进行稀释。稀释方法为在溶解后的溶液中再加入5%葡萄糖注射液或0.9%氯化钠注射液4ml，制得6ml青蒿琥酯肌肉注射用溶液，每ml该溶液含青蒿琥酯20mg，反复振摇至完全溶解澄清后方可使用。如配制过程中出现浑浊或沉淀物不可使用。

配制时注意：

由于青蒿琥酯在水溶液中不稳定，配制的溶液必须在配制后1小时使用。如果超过1小时未使用，应弃之。如配制过程中出现浑浊或沉淀物不可使用。

【不良反应】

1、本品最主要的不良反应是罕见的严重过敏反应（约1人/3000），病人出现荨麻疹及其他症状，包括瘙痒、水肿、低血压和呼吸困难。

2、本品静脉注射后可见头晕、轻度头痛、出疹和味觉改变（金属味或苦味）等症状较轻的不良反应，也有恶心、呕吐、厌食和腹泻等报告。然而这些症状不能确定是否是重症疟疾的症状。

3、依据目前的观察数据和文献报道，认为至少与青蒿琥酯有关的不良反应按身体系统、器官分类和发生频数列表如下，分为非常普遍(≥ 1/10)、普遍(1/100－1/10)、不普遍(1/1 000－1/100)、罕见(1/10 000－1/1 000)和非常罕见(< 1/10 000)。

血液和淋巴系统

不普遍：中性粒细胞减少和贫血（二者都是偶尔严重）、血小板减少。

非常罕见：单纯红细胞再生障碍。

频次未知：治疗后贫血（见下面）、轻度和一过性的网织红细胞计数下降。

神经系统

普遍：头晕、轻度头痛、头痛、失眠、耳鸣（听力功能有下降或没有下降）。

非常罕见：周围神经病变（或感觉异常）。

呼吸系统

不普遍：咳嗽、鼻部症状。

胃肠道

普遍：味觉异常、恶心、呕吐、腹痛或痉挛、腹泻。

罕见：出现血清淀粉酶。

肝胆

不普遍：肝转氨酶一过性升高(AST，ALT)。

罕见：肝炎。

皮肤和皮肤软组织

不普遍：出疹、脱发

肌肉、骨骼和结缔组织

不普遍：关节痛、肌疾病

一般反应和用药部位

普遍：疲劳、不适感和注射部位疼痛。

免疫系统

不普遍：过敏。

治疗后贫血

一般情况下，尽管网织红细胞计数一过性下降，但在临床研究的重症疟疾中归因于静注青蒿琥酯的严重贫血临床上并不普遍。然而在欧洲一组重症疟疾病人采用青蒿琥酯静注治疗的25例中，6例在治疗后2-4周发生溶血性贫血，其中5例需要输血，溶血的病因不详。

【禁忌】

对青蒿琥酯或其他青蒿素类过敏的患者禁用。

【注意事项】

1、与口服治疗的相互转化

使用Artesun®治疗重症疟疾，当病人症状缓解可以口服给药后，应继续给予足量的适宜口服复方抗疟药联合治疗。

2、耐药性

选择与Artesun®合用的适宜联合治疗药物时，应考虑当地疟疾耐药性流行率的相关信息。

3、治疗后贫血

除了网织红细胞短暂性降低之外，临床试验未表明静脉用青蒿琥酯会引发显著的贫血症状。但也有报告非常少见的治疗后出现溶血性贫血，需要输血治疗的案例。

4、肝/肾功能不全

应用青蒿琥酯于肝肾功能不全患者的药物动力学数据较有限。依据疟疾病人进行研究以及已知代谢作用的数据，无需为肝/肾功能不全患者进行剂量调整。

5、儿科群体

临床试验表明，无论是成人与儿童，通过静脉或肌肉给予青蒿琥酯注射，其疗效与安全性均相近。

6、驾车与使用机器

尚无使用青蒿琥酯对驾车与使用机器影响的参考信息。如需驾车与使用机器，应考察患者的临床表现/状态。

【孕妇及哺乳期妇女用药】

孕期妇女：

恶性疟对于妊娠期妇女尤其危险，因而必须及时给予足剂量的非肠道抗疟药治疗。

对于妊娠期妇女使用青蒿琥酯进行治疗的临床经验不多。在动物实验中，注射用青蒿琥酯对于孕早期动物（相当于人怀孕头三个月）有一定的胚胎毒性。但孕早期临床安全研究数据至今尚不能表明此治疗会对胎儿造成更大风险的伤害。因此，临床使用时应权衡利弊。如需挽救早期孕妇的生命，则应给予注射用青蒿琥酯治疗。对于其他人群，也应有青蒿琥酯具有相对其他治疗药物更好降低恶性疟死亡率的意识。

在泰国进行的一项研究，使用青蒿素类药物（青蒿琥酯为主）对461名孕妇（其中44人为妊娠早期）进行治疗，结果表明414名正常生产的孕妇身上未出现显著副反应。所观察到的流产、死胎、先天异常与体重不足发生率与普通人群无异。

1999年至2006年间，在泰国、冈比亚与苏丹对于2045名孕妇进行了药物治疗，使用青蒿琥酯单方或青蒿琥酯与其他抗疟药（如奎宁、甲氟喹、阿托喹酮-氯胍以及磺胺多辛-乙胺嘧啶）联合使用。大部分孕妇为4～9个月孕期，通过一年的观察表明，新生儿体重、妊娠期、胎盘重、先天异常率以及婴儿生长与发育指标等参数均与普通人群无显著差异。

哺乳期妇女：

有限的证据表明在哺乳期妇女的乳汁中有低量的青蒿琥酯活性代谢物-双氢青蒿素存在。此微量药物既不会引起哺乳期婴儿不良反应，也不会给予婴儿足够的抗疟保护。

【儿童用药】见【用法用量】。

【老年用药】见【用法用量】。

【药物相互作用】

通过血浆与红细胞酯酶，青蒿琥酯可迅速在体内转化为活性代谢物-双氢青蒿素（DHA）。DHA的消除过程也非常迅速（约30～45分钟的半衰期），因此药物-药物相互作用的几率较有限。在体外药物相互作用研究中，发现青蒿琥酯对细胞色素P450同工酶的影响非常小。

一些已开展的临床药物-药物相互作用的研究，也未发现显著的相互作用。

【药物过量】

青蒿琥酯急性用药过量的经验有限。1例5岁的儿童在未注意的情况下过量使用青蒿琥酯栓剂88 mg/kg/day，连用4天，比推荐的青蒿琥酯栓最高剂量高7倍，过量引起全血细胞减少、黑粪、癫痫发作、多器官衰竭并死亡。

药物过量的处置应包括一般的支持措施。

【临床试验】

青蒿琥酯静脉注射健康人试验表明，分别于0、4、24、48h给予成人每次3.75mg/kg静脉注射，除了给药第3天出现网织红细胞一过性轻度下降（在正常值范围内）外，未发现其他不良反应。

临床上采用青蒿琥酯静脉注射成人首剂120mg（2.4mg/kg，红细胞原虫感染率≥5%时，4～6h再给予60mg）、第24、48h再分别给予60mg(1.2mg/kg)三天疗法；或首剂给药后，每天再给予60mg，连续6天的七天疗法治疗疟疾病人（特别是重症疟疾）时，均取得非常好的疗效。

在SEAQUAMAT（东南亚/南亚奎宁与青蒿琥酯治疗疟疾比较研究）中，在孟加拉、印度、印度尼西亚和缅甸进行了多国、随机、开放、多中心的研究，1461例重症疟疾病人（包括1259例成人）静注青蒿琥酯或奎宁治疗。青蒿琥酯IV给药，于第0、12和24小时按每公斤体重注射2.4mg，然后一日一次，直至病人可以口服药物。奎宁IV给药，20mg/kg起始剂量输注4小时，然后10mg/kg输注2-8小时，一日3次，直至病人可以口服药物。青蒿琥酯治疗组的病人死亡率是15%，奎宁组是22%；降低死亡风险 34.7%（p=0.0002）。亚组分析提示在原虫血症>10%的病人中青蒿琥酯的优势强于奎宁。202例儿科病人（低于15岁）的死亡率降低与总的结果相符，但一些儿童的年龄太小无法证明统计学显著性。IV青蒿琥酯耐受好，而奎宁则有潜在的低血糖风险。

儿科

AQUAMAT（非洲奎宁与青蒿琥酯治疗疟疾比较研究）是一个多国、随机、开放、多中心的研究，探寻扩大SEAQUAMAT的研究结果，比较非肠道给予青蒿琥酯对奎宁治疗严重疟疾，在9个非洲国家的5425例非洲儿童（小于15岁）中进行。像SEAQUAMAT一样给药，除了都给与青蒿琥酯和奎宁静注或肌注，每种药使用相同的IM和IV剂量，大致有三分之一的病人肌注研究药。青蒿琥酯组的病人死亡率8.5%，相比奎宁组为10.9%，死亡的相对危险下降22.5%，（ p=0.0022），IV和IM的风险下降相似。此外，两组生存者治疗后28天的神经学后遗症发生无显著差异，像在SEAQUAMAT一样，治疗后的低血糖在奎宁治疗组的发生更普遍。

【药理毒理】

药理作用

青蒿琥酯为双氢青蒿素半琥珀酸酯衍生物，由青蒿素还原而得。青蒿素是从传统的中药青蒿（Artemisia annua L.）中提取的倍半萜内酯内过氧化物。

在青蒿素分子结构与其抗疟活性的关系研究中，最为肯定的结果是分子必须有过氧基团，无过氧基团将失去抗疟活性。一般认为，青蒿素类抗疟药特异性地浓集在疟原虫细胞内，而疟色素中的二价铁能催化分解青蒿素的过氧基团产生自由基，从而对疟原虫的膜系统或生命大分子产生氧化损伤。电镜观察表明，青蒿素首先作用于疟原虫红内期滋养体的食物泡膜、表膜和线粒体，其次是核膜和内质网。此外，对核内染色体也有一定影响。由于食物泡膜发生变化阻断了疟原虫摄取营养的早期阶段，使疟原虫迅速发生氨基酸饥饿，形成自噬泡，并不断排出体外，使胞浆大量损失，内部结构瓦解而死亡。

青蒿素对疟原虫红内期的无性体（环状体、滋养体、裂殖体）具有杀灭作用，起效迅速，16～20小时左右可清除95%左右的疟原虫；对有性体（配子体Ⅰ、Ⅱ、Ⅲ、Ⅳ期）有抑制作用。

在体外研究中青蒿琥酯的活性代谢物双氢青蒿素显示对恶性疟抗氯喹虫株和敏感株有同样的作用。

青蒿琥酯及其他青蒿素类药实际上对红外期的原虫、子孢子、肝裂殖体或裂殖子无作用。

毒理研究

一般毒性：

大鼠连续7天肌肉注射青蒿琥酯50 mg/kg/天，犬连续28天经口给予青蒿琥酯82.5 mg/kg/天（以mg/kg/天计，分别约为人推荐最大剂量的10倍和17倍），可见明显的造血器官、免疫系统和肝肾毒性。

遗传毒性：

青蒿琥酯在体外和体内试验(Ames试验、小鼠微核试验)中未见致诱变性和致染色体断裂作用。

生殖毒性：

大鼠、兔和猴经口给予青蒿琥酯可见剂量依赖的胚胎毒性，导致胚胎吸收和流产，及低发生率的心脏和骨骼缺陷。妊娠猴未见明显毒性反应剂量(NOAEL)为12 mg/kg（暴露3～7天）；妊娠大鼠和妊娠兔未见毒性反应或轻微毒性反应剂量为5～7 mg/kg（暴露12天）。这两个剂量均高于治疗剂量(2.4mg/kg)，暴露时间均超出重症疟疾患者治疗预期暴露的持续时间。大鼠妊娠第9～14天的胎鼠对青蒿琥酯最敏感，其他时段胚胎毒性明显下降。

安全药理学：

青蒿琥酯单次静脉注射200mg/kg（小鼠），450 mg/kg（大鼠、兔、犬），之后雄性大鼠又单次经口给予180 mg/kg后可见有轻微的镇静作用，体温下降，轻度尿钠排泄作用和肌酐清除率下降。犬连续14天静脉注射青蒿琥酯10mg/kg、20mg/kg和50mg/kg，未见明显的临床症状，包括神经系统、体重、心电图（包括QT间期变化）、心率、血压或呼吸的变化。

【药代动力学】

静脉注射

静脉注射青蒿琥酯后快速生物转化为活性代谢物双氢青蒿素；青蒿琥酯的半衰期（$t_{1/2}$）不到5分钟。在对加蓬重症疟疾儿童的研究中单次IV剂量2.4 mg/kg，青蒿琥酯血药浓度峰值（Cmax）77 µmol/L，在越南无并发症疟疾成人中是42 µmol/L和36 µmol/L。

青蒿琥酯IV 5分钟内血液中见高浓度的DHA，DHA的达峰时间(Tmax)和$t_{1/2}$范围分别是0.5～15 分钟和21～64分钟，DHA　Cmax范围5.3～10.6 µmol/L。

肌肉注射

肌注青蒿琥酯后吸收迅速，通常注射后30分钟内达峰值。在加蓬儿童和越南成人IM给药2.4 mg/kg后吸收很快，Tmax分别为8和12分钟，相应的$t_{1/2}$儿童为48分钟，成人为41分钟，Cmax分别为1.7和 2.3µmol/L。肌注青蒿琥酯和静注比较Cmax儿童和成人分别为1/45和1/20，消除率分别为32倍和13倍。

分布

研究证明双氢青蒿素在恶性疟感染的红细胞中大量聚集，双氢青蒿素的血浆蛋白结合在病人中是93%，健康志愿者中是88%。

代谢和消除

青蒿琥酯被血浆酯酶类广泛而快速水解，代谢物双氢青蒿素在口服青蒿琥酯中的抗疟作用强，然而静注给药后青蒿琥酯的作用更强，双氢青蒿素在肝脏通过葡萄苷酸化进一步代谢，经尿排泄；在恶性疟病人的主要尿产物中鉴定出α-双氢青蒿素-β-葡糖苷酸。

特殊人群

目前尚缺乏肝肾功能低下病人的药代动力学数据。然而，根据已知的青蒿琥酯代谢和消除机制，结合重症疟疾病人的临床数据和伴有不同程度肾或肝损害的数据，在肝肾功能损害的情况下不必考虑改变剂量。

【贮藏】

低于30℃遮光存放。

配制后的溶液应存放低于30℃，并应在1小时内使用。

【包装】

包装：每盒装1瓶注射用青蒿琥酯、1支碳酸氢钠注射液(50mg/ml)和1支氯化钠注射液(9mg/ml)。

低硼硅玻璃管制注射剂瓶加注射用无菌粉末用卤化丁基橡胶塞（瓶塞外压轧铝塑盖）。

7ml、15ml分别装注射用青蒿琥酯 60mg、120mg

低硼硅玻璃安瓿瓶1 ml、2ml分别装碳酸氢钠注射液(50mg/ml) 1ml 、2ml

低硼硅玻璃安瓿瓶5 ml、10ml分别装氯化钠注射液(9mg/ml) 5ml 、10ml

【有效期】 1）60mg　36 个月
2）120mg　12 个月

【执行标准】1）60mg　中国药典2015年版二部
2）120mg 中国药典2015年版二部+药品补充申请批件（批件号2013B01523）

【批准文号】1）60mg　国药准字H10930195
2）120mg　国药准字H20133237

【生产企业】

企业名称：桂林南药股份有限公司
生产地址：桂林市七里店路43号
邮政编码：541004
电话：0773-3841973
传真：0773-3841973
网址：http://www.guilinpharma.com

4.6.04.23.024.01.04

Artesun®

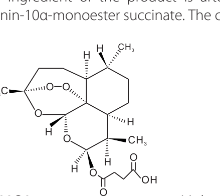
Artesunate for Injection

Please read the instruction carefully and use the medicine under the guidance of doctors.

[Name of the medical product]

Common name: Artesunate for InjectionTrade name: Artesun®English name: Artesunate for injectionChinese pinyin: Zhusheyong Qinghaohuzhi

[Ingredients] The main ingredient of the product is artesunate, and the chemical name of which is dihydroartemisinin-10α-monoester succinate. The chemical structural formula is as followed:



Molecular formula: C19H28O8　　Molecular weight: 384.42

[Description] White crystalline powder.

Solvent (sodium bicarbonate injection): Clear, colorless liquid

Solvent (sodium chloride injection): Clear, colorless liquid

[Therapeutic indication] Artesun® is indicated for treatment of cerebral malaria and all other kinds of severe malarias.

[Qualitative and quantitative composition]

1) Each Artesun® 60 mg box contains 1 vial of 60 mg artesunate powder for solution for injection, 1ampoule of 1 mL sodium bicarbonate 50 mg/mL solution for injection and 1ampoule of 5mL sodium chloride 9 mg/mL solution for injection.

2) Each Artesun® 120 mg box contains 1 vial of 120 mg artesunate powder for solution for injection, 1 ampoule of 2 mL sodium bicarbonate 50 mg/mL solution for injection and 10mL sodium chloride 9 mg/mL solution for injection.

[Posology and method of administration]

Method of administration

The product is administered by intramuscular (IM) or intravenous (IV) injection, but should not be administered as an intravenous drip.

Before administration, the artesunate powder must be dissolved in the supplied 5% sodium bicarbonate solvent first, and then diluted with 5% glucose injection or 0.9% sodium chloride injection to obtain a reconstituted artesunate solution of a certain concentration for administration.

For intramuscular (IM) injection, withdraw the required volume of artesunate solution and then inject intramuscularly. The anterior thigh is usually the preferred site for injection. If the total volume of solution to be injected intramuscularly is large, it may be preferable to divide the volume and inject it at several sites, e.g. both thighs.

For intravenous (IV) injection, withdraw the required volume of artesunate solution and then inject slowly intravenously, over 1-2minutes.

It is especially cautioned that either by intravenous (IV) or intramuscular (IM) injection, the product should not be mixed with other medicines for administration due to lack of relevant study data.

Dose and dosage regimen

For adult: Artesun® is administered at a dose of 120mg (2.4 mg of artesunate/ kg of body weight), by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours respectively, and then once daily till oral treatment can be tolerated.

Artesun® should be administered for a minimum of 24 hours (3 doses), regardless of the patient's earlier recovery of the ability to tolerate oral medication. After at least 24 hours of Artesun®, and when the patient is able to tolerate oral medication, he/she should be switched to a complete treatment course of an oral combination antimalarial regimen. The oral medication should be administered in accordance with the combination antimalarial regimen.

For children: each dose for children should be determined as per the body weight, and the recommended dose is listed in the following table. The equal volume of the determined dose could be continued for administration once daily based on the needs till the 7 day. Or when the patient is in remission and recover the ability to tolerate oral medication, he/she should be switched to a complete treatment course of an oral combination antimalarial regimen. The oral medication should be administered in accordance with the combination antimalarial regimen.

Dosage of administration of Artesunate for Injection for Children (mg)

Age group (years)	The 1st day		The 2nd day
	0 hour	12 hours	24 hours
≥16	120mg	120mg	120mg
11~	90mg	90mg	90mg
7~	60mg	60mg	60mg
＜7	2.4/kg	2.4/kg	2.4/kg

Preparation

For intravenous (IV) injection:

When the product of 60mg strength is applied, using a syringe, withdraw 1mL of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing 60mg of the artesunate powder. Shake the vial for several minutes to mix well till the powder is completely dissolved and the solution is clear before dilution. For dilution, add either 5mL of 5% glucose for injection or the same volume of 0.9% sodium chloride for injection to the vial containing the reconstituted artesunate solution to obtain 6mL of artesunate solution for intravenous injection. This will yield a solution containing artesunate 10 mg/mL. Shake to mix well, ensuring that the resulting solution is still clear before administration. If the solution appears cloudy or a precipitate is present, it should be discarded.

When the product of 120mg strength is applied, using a syringe, withdraw 2mL of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing 120mg of the artesunate powder. Shake the vial for several minutes to mix well till the powder is completely dissolved and the solution is clear before dilution. For dilution, add either 10mL of 5% glucose for injection or the same volume of 0.9% sodium chloride for injection to the vial containing the reconstituted artesunate solution to obtain 12mL of artesunate solution for intravenous injection. This will yield a solution containing artesunate 10 mg/mL. Shake to mix well, ensuring that the resulting solution is still clear before administration. If the solution appears cloudy or a precipitate is present, it should be discarded.

For intramuscular (IM) injection:

When the product of 60mg strength is applied, using a syringe, withdraw 1mL of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing 60mg of the artesunate powder. Shake the vial for several minutes to mix well till the powder is completely dissolved and the solution is clear before dilution. For dilution, add either 2mL of 5% glucose for injection or the same volume of 0.9% sodium chloride for injection to the vial containing the reconstituted artesunate solution to obtain 3mL of artesunate solution for intramuscular injection. This will yield a solution containing artesunate 20 mg/mL. Shake to mix well, ensuring that the resulting solution is still clear before administration. If the solution appears cloudy or a precipitate is present, it should be discarded.

When the product of 120mg strength is applied, using a syringe, withdraw 2mL of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing 120mg of the artesunate powder. Shake the vial for several minutes to mix well till the powder is completely dissolved and the solution is clear before dilution. For dilution, add either 4mL of 5% glucose for injection or the same volume of 0.9% sodium chloride for injection to the vial containing the reconstituted artesunate solution to obtain 6mL of artesunate solution for intramuscular injection. This will yield a solution containing artesunate 20 mg/mL. Shake to mix well, ensuring that the resulting solution is still clear before administration. If the solution appears cloudy or a precipitate is present, it should be discarded.

Precaution in preparation:

Because of the instability of artesunate in aqueous solutions, the reconstituted solution must be used within one hour of preparation, otherwise it should be discarded. If the solution appears cloudy or a precipitate is present, it should be discarded.

[Undesirable effects]

1. The most important reported side effect of artesunate is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, including pruritus, oedema, hypotension, and/or dyspnoea.

2. More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria.

3. According to the available observation data and literature reports, adverse events considered at least possibly related to artesunate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100-1/10), uncommon (1/1,000-1/100), rare (1/10,000-1/1,000), and very rare (< 1/10,000).

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia Frequency

unknown: Post-treatment anaemia (see below), mild and transient decrease in reticulocyte count

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function)

Very rare: Peripheral neuropathy (or paraesthesia)

Respiratory disorders

Uncommon: Cough, nasal symptoms

Gastrointestinal disorders

Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Raised serum amylase, pancreatitis

Hepatobiliary disorders

Uncommon: Transient rises in liver transaminases (AST, ALT)

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Uncommon: Rash, alopecia

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, muscle disorders

General disorders and administration site conditions

Common: Fatigue, discomfort, pain at injection site

Immune system disorders

Uncommon: hypersensitivity

Post-treatment anaemia

In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting in 2 to 4 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

[Contraindications]

Artesun® is contraindicated in patients with hypersensitivity to artesunate or other artemisinins.

[Special warnings and precautions for use]

1. Switching to oral treatment regimen

Acute treatment of severe falciparummalaria with Artesun® should always be followed by a complete treatment course of an appropriate oral combination antimalarial Regimen.

2. Resistance to antimalarials

Local information on the prevalence of resistance to antimalarials should be considered in choosing the appropriate combination antimalarial regimen for use with Artesun®. Relevant treatment guidelines should be consulted.

3. Post-treatment anaemia

Despite transient decreases in reticulocyte counts, clinically significant anaemia associated with IV artesunate has not been common in clinical trials. However, occasional cases of post-treatment haemolytic anaemia severe enough to require transfusion have been reported.

4. Hepatic/ renal impairment

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited. Based on data from studies in patients with severe malaria, as well as the known metabolism of artesunate, dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

5. Pediatric population

In clinical trials, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adult and pediatric populations.

6. Effects on ability to drive and use of machines

There is no information on the effect of artesunate on the ability to drive or use machines. The patient's clinical status should be considered when assessing ability to drive or operate machinery.

[Pregnancy and lactation]

Pregnancy:

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral antimalarial treatment should be administered without delay.

There has been limited clinical experience with the use of artesunate in pregnancy. In animal studies, artesunate has been associated with fetal toxicity during the first trimester of pregnancy (equivalent to the first trimester of pregnancy of human). To date, clinical data regarding safety in the first trimester have not indicated an increased risk of foetal harm. Treatment with artesunate should not be withheld during the first trimester if it is potentially life-saving for the mother. As in other populations, the evidence that artesunate reduces the risk of deathfrom severe malaria compared to other treatments should be borne in mind.

In a study of 461 pregnant Thai women (44 in their first trimester) who were treated with artemisinins (predominantly artesunate), there was no obvious evidence of adverse effects amongst the 414 women for whom pregnancy outcomes were known. The observed rates of abortion, stillbirth, congenital anomalies and low birth weight were comparable to community rates.

In clinical trials from 1999 to 2006, 2045 pregnant women in Thailand, the Gambia, and Sudan were treated with artesunate, either alone or in combination with other antimalarials, including quinine, mefloquine, atovaquone-proguanil and sulfadoxine-pyrimethamine. In these patients, most of whom were in their second or third trimesters of pregnancy, there were no significant differences compared to the general community in birth weights, duration of gestations, placental weights, or rates of congenital abnormalities, or in growth and developmental parameters of infants monitored for one year.

Breastfeeding / lactation

Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low levels in breast milk. The drug levels are not expected to cause any adverse effects in breastfed infants. The amount of drug present in breast milk does not protect the infant from malaria.

[Use for children] see **[Posology and method of administration]**

[Use for elders] see **[Posology and method of administration]**

[Interaction with other medicinal products and other forms of interaction]

Artesunate is rapidly and extensively converted to dihydroartemisinin (DHA), the active metabolite, primarily by plasma and erythrocyte esterases. DHA elimination is also rapid (half-life approximately 45 min) and the potential for drug-drug interactions appears limited. In vitrodrug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes.

Few clinical drug-drug interaction studies have been performed, however noclinically significant interactions have been identified.

[Overdose]

Experience of acute overdose with artesunate is limited. A case of overdose has been documented in a 5-year-old child who was inadvertently administered rectal artesunate at a dose of 88 mg/kg/day over 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose. The overdose was associated with pancytopenia, melena, seizures, multiorgan failure and death. Treatment of overdose should consist of general supportive measures.

[Clinical testing]

The trial on healthy volunteers who are administered with artesunate injection intravenously indicated that when the adults are administered with intravenous injection at a dose of 3.75mg/kg at 0, 4, 24 and 48 hours respectively, no adverse effect has been observed other than a mild and transient decrease in reticulocyte count (within the range of normal value) on the 3rd day.

Both 3-day regimen of artesunate administered intravenously to adults at the initial dose of 120mg (2.4 mg/kg, while parasites in infected erythrocyte ≥5%, 60mg at 4~6h once more) and 60mg (1.2mg/kg) at 24 and 48 hours respectively and 7-day regimen of initial dosing followed by 60mg daily for successive 6 days for the treatment of malaria (especially for severe malaria) obtained very good results.

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parasitemia >10%. The reduction in mortality observed in the 202 pediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. IV artesunate was well tolerated, while quinine was associated with a substantially increased risk of hypoglycaemia.

Pediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries. Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

[Pharmacological and toxicological properties]

Pharmacological action

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, Artemisia annua L.), a plant which has been used for centuries in traditional Chinese medicine.

According to study on the relationship between the molecular structure and the antimalarial activity of artemisinin, it is most certain that the molecule must comprise an endoperoxide bridge, the lack of which will result in a loss of antimalarial activity. As a general acknowledgement, the artemisinin-based antimalarials concentrate specifically inside the parasite cell. Catalyzed by the Fe2+ in the malarial haeme, the peroxide bridge of artemisinins is cleaved, thereby generating free radicals, which may cause damage by oxidization on the membrane system or the bio-macromolecules of the plasmodium.

According to observation by electronic microscope, artemisinins first act on the food vacuole membrane, pellicle and mitochondria in the trophozoite during erythrocytic stage of malaria parasite, and then on the nuclear membrane and endoplasmic reticulum. In addition, it also influences the chromosome within the nuclear. Since the altered food vacuole membrane cuts off the early stage of nutrition intake, the malaria parasite develop immediate starvation for amino acid, forming autophagic vacuole and discharging constantly, which causes massive loss of cytoplasm, disruption of the internal structure and death as a result. Artemisinins have the ability to kill the phorozoons (ring stage, and schizonts) in erythrocytic stage of malaria parasite with rapid acting, presenting clearance of about 95% of malaria parasite in 16~20 hours; and have inhibition effect on the zoogamy body (stage I, II, III, IV of gametophyte).

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of P. falciparum.

Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

Toxicological study

General toxicity:

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system andresponse, the liver and kidneys.

Genotoxicity:

Artesunate did not show any mutagenic or clastogenic potential in in vitroand in vivotests (Ames, mouse micronucleus).

Reproductive toxicology studies:

Oral artesunate caused dose-dependent foetal toxicity in rats, rabbits and monkeys, resulting in foetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3 and 7 day exposures) and theno or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12 day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced.

Safety pharmacology studies:

A slight sedative effect, decrease in body temperature, mild natriuretic effect and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs) and following single oral doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20, 50, and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

[Pharmacokinetic properties]

Intravenous

After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life ($t_{1/2}$) is estimated to be less than 5 minutes. Following a single IV dose of 2.4 mg/kg, maximum artesunate plasma concentrations (Cmax) were estimated to be 77 µmol/L in a study in Gabonese children with severe malaria, and 42 and 36 µmol/L in two studies in Vietnamese adults with uncomplicated malaria. High concentrations of DHA are observed within 5 minutes of artesunate IV administration. In the above studies (adult and paediatric), the ranges of values for the estimated time to maximum concentration (Tmax) and $t_{1/2}$ for DHA were 0.5-15 minutes and 21-64 minutes, respectively, while DHA Cmax values ranged from 5.3-10.6 µmol/L.

Intramuscular

Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. Thus, after IM injection of 2.4 mg/kg of artesunate, absorption was rapid in Gabonese children and Vietnamese adults, with Tmax values of 8 and 12 minutes, respectively. The corresponding artesunate t1/2 values were estimated to be 48 minutes in children and 41 minutes in adults, and Cmax values were1.7 and 2.3 µmol/L, for children and adults, respectively. After IM injection artesunate Cmax values were therefore lower by roughly 45-fold in children and 20-fold in adults when compared to IV injection. However, rates of artesunate elimination in children and adults were 32-fold and 13-fold slower, respectively, following IM injection, compared to IV administration.

Distribution

DHA has been shown to substantially accumulate in P. falciparum-infected erythrocytes. Plasma protein binding of dihydroartemisinin was determined to be 93% in patients and 88% in healthy volunteers.

Metabolism and elimination

Artesunate is extensively and rapidly hydrolysed by plasma esterases, with possible minimal contribution by CYP2A6. The main metabolite, dihydroartemisinin, accounts for most of the in vivo antimalarial activity of oral artesunate, however, following IV administration. artesunate may contribute more significantly. DHA is further metabolized in the liver via glucuronidation and is excreted in the urine; α-dihydroartemisinin-β-glucuronide has been identified as the major urinary product in patients with falciparum malaria.

Special population

No pharmacokinetic data are available for patients with impaired renal or hepatic function. However, based on the known mechanisms of metabolism and elimination of artesunate, combined with clinical data from patients with severe malaria and accompanying renal and/or hepatic compromise of various degrees, no dose modifications are considered necessary in renal or hepatic impairment.

[Storage]

Store below 30℃. Protect from light.

The reconstituted solution should be stored below 30℃ and should be used within 1 hour.

[Packaging]

Pack size: A carton box containing one vial of artesunate for injection, one ampoule of the sodium bicarbonate solvent (50mg/mL) and one ampoule of the sodium chloride solvent (9mg/mL).

Artesunate for injection (60mg and 120mg): low borosilicate glass vial for injection with halogenated butyl rubber stoppers used for sterile powder for injection (further capped with aluminium lid with a blue flip-off plastic cover).

Artesunate for injection of 60mg and 120mg are filled in the glass vials of 7mL and 15mL respectively.

Solvent (sodium bicarbonate injection 50mg/mL) of 1mL and 2mL are filled in the low borosilicate glass ampoules of 1mL and 2mL respectively.

Solvent (sodium chloride injection 9mg/mL) of 5mL and 10mL are filled in the low borosilicate glass ampoules of 5mL and 10mL respectively.

[Shelf life] 1) 60mg　36 months
2) 120mg　12 months

[Product standard] 1) 60mg　Part II of Chinese Pharmaceutical Edition 2015
2) Part II of Chinese Pharmaceutical Edition 2015 and Drug Supplemental Approval (Approval No.: 2013B01523)

[Approval number] 1) 60mg　National Drug Approval No. H10930195
2) 120mg　National Drug Approval No. H20133237

[Supplier]

Name of the manufacturer: Guilin Pharmaceutical Co., Ltd.
Address: No. 43 Qilidian Road, Guilin 541004, Guangxi, China
Tel: 0086-773-3841973
Fax: 0086-773-3841973
Web: http://www.guilinpharma.com