

## Access to Artemisinin-based Antimalarial Medicinal Products of Acceptable Quality

### Prequalification Programme

**SUPPLIERS WHOSE ARTEMISININ-BASED ANTIMALARIAL MEDICINES HAVE BEEN FOUND ACCEPTABLE, IN PRINCIPLE, FOR PROCUREMENT BY UN AGENCIES.**

Please note, that the prequalified medicines listed below are intended to use according to the WHO Guidelines for the Treatment of Malaria (WHO, 2006), available at <http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf>, according to which uncomplicated falciparum malaria should be treated with combination therapy, and not by artemisinin alone or any other monotherapy.

**Date: 30 August 2007**

*This list is the 6<sup>th</sup> version. The list will be regularly updated and each change on the current version is labeled in blue. Kindly ensure that the most current list is used. For changes to the list, see Table 1: Version history (below the "List")*

**List 1: Alphabetical list of prequalified products manufactured at the specified manufacturing sites**

Ref. N°	International Nonproprietary Name (INN)	Strength	Dosage form	Supplier	Manufacturing site		Packaging material and pack	
018	Artesunate	50mg	Tablets	Sanofi-Synthelabo, Gentilly, France	Guilin Pharmaceutical Co. Ltd, Guangxi	P. R. China	Blister	25 blister of 12
026	Artemether + Lumefantrine	20mg + 120mg	Tablets	Novartis Pharma, Basel, Switzerland	Beijing Novartis Pharma, Beijing  Novartis Pharmaceuticals Corporation Suffern	P. R. China  USA	Blister	30 blisters of  6, 12, 18 or 24

027	Artemotil	50mg/ml	Sol inj	ARTECEF BV Zeewolde The Netherlands	Rotexmedica GmbH Tritau	Germany	Ampoules	10 or 100 ampoules each of 1ml
028	Artemotil	150mg/ml	Sol inj	ARTECEF BV Zeewolde The Netherlands	Rotexmedica GmbH Tritau	Germany	Ampoules	10 or 100 ampoules each of 1ml
038	Artesunate	50mg	Tablets	Ipca Laboratories Ltd	Dadra and Nagar Haveli (U.T.)	India	PVdC/Alu	12
044	Artesunate	50mg	Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P.R. China	PVC/Al blister	12
045	Amodiaquine	150mg	Film-coated Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P. R. China	PVC/Alu blisters  Cardboard box	6  2 x 6
046	Artesunate + Amodiaquine	50mg + 150mg	Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P. R. China	PVC blisters sealed with an aluminium foil lid  Cardboard box	4 + 4  3 x (4+4)

### Version History

Edition		Date		Change				
<b>6<sup>th</sup> Edition of the List</b>		<b>30 August 2007</b>		<b>Add to the List:</b>				
038	Artesunate	50mg	Tablets	Ipca Laboratories Ltd	Dadra and Nagar Haveli (U.T.)	India	PVdC/Alu	12
045	Amodiaquine	150mg	Film-coated Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P. R. China	PVC/Alu blisters Cardboard box	6 2 x 6
046	Artesunate + Amodiaquine	50mg + 150mg	Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P. R. China	PVC blisters sealed with an aluminium foil lid Cardboard box	4 + 4 3 x (4+4)
Edition		Date		Change				
<b>5<sup>th</sup> Edition of the List</b>		<b>29 March 2006</b>		<b>Add to the List:</b>				
<i>The ONLY new addition to the 5<sup>th</sup> Edition concerning product 026 is the introduction of the manufacturing site Novartis Pharmaceuticals Corporation in Suffern, USA (Highlighted in grey)</i>								
026	Artemether + Lumefantrine	20mg 120mg	Tablets	Novartis Pharma Basel Switzerland	Beijing Novartis Pharma Beijing  Novartis Pharmaceuticals Corporation Suffern	P.R. China  USA	Blister	30 blisters of 6, 12, 18 or 24

Edition		Date		Change				
<b>4<sup>th</sup> Edition of the List</b>		<b>1 March 2006</b>		<b>Add to the List:</b>				
027	Artemotil	50mg/ml	Sol inj	ARTECEF BV Zeewolde The Netherlands	Rotexmedica GmbH Tritau	Germany	Ampoules	10 or 100 ampoules each of 1ml
028	Artemotil	150mg/ml	Sol inj	ARTECEF BV Zeewolde The Netherlands	Rotexmedica GmbH Tritau	Germany	Ampoules	10 or 100 ampoules each of 1ml
Edition		Date		Change				
<b>3<sup>rd</sup> Edition of the List</b>		<b>21 December 2005</b>		<b>Add to the List:</b>				
044	Artesuante	50mg	Tablets	Guilin Pharmaceutical Co., Ltd	Guilin, Guangxi	P.R. China	PVC/Al Blister	12
Edition		Date		Change				
<b>2<sup>nd</sup> Edition of the List</b>		<b>26 April 2004</b>		<b>Add to the List:</b>				
018	Artesunate	50mg	Tablets	Sanofi-Synthelabo, Gentilly, France	Guilin Pharmaceutical Co. Ltd, Guangxi	China	Blister	12
026	Artemether + Lumefantrine	20mg 120mg	Tablets	Novartis Pharma, Basel, Switzerland	Beijing Novartis Pharma Beijing	China	Blister	30

3 <sup>rd</sup> Edition of the List		16 November 2005		Add to the List:				
027	Artemotil	50mg/ml	Injections	ACE Pharmaceuticals BV	Rotexmedica GmbH Tritau	Germany	Vial	1ml
028	Artemotil	150mg/ml	Injections	ACE Pharmaceuticals BV	Rotexmedica GmbH Tritau	Germany	Vial	1ml

### Background:

A "*Procurement, Quality and Sourcing Project: Access to Artemisinin-based Combination Antimalarial Drugs of acceptable quality*" was actively started by WHO in collaboration with other United Nations Organizations (UNICEF, and UNDP) in April 2002 as part of the Roll Back Malaria project. This is now known as "Prequalification Programme". The background to the programme is described in the **programme description**.

The procedure for assessing the acceptability in principle of *Artemisinin-based Combination Antimalarial* drugs comprises various components including 1) The evaluation of product data and information provided by manufacturers and suppliers, and 2) Inspection of manufacturing sites.

Due to the particular properties of several substances used in some pharmaceutical finished dosage forms in the treatment of Malaria (e.g. some Artemisinin derivatives), and where there are only Pharmacopoeia monographs and standards available for some substances and finished products, WHO appointed experts performed a comprehensive and rigorous evaluation of the products included in the list, with a view to establishing their compliance with international standards (see below).

### Objective

The objective of the programme, is to assess the acceptability in principle of *Artemisinin-based Combination Antimalarial* drugs for procurement by UN Agencies. The assessment procedure is aimed at identifying products and manufacturers meeting WHO standards (see below). Thus, the programme facilitates the procurement of *Artemisinin-based Combination Antimalarial* related drugs of acceptable quality.

## Method followed for prequalification

In assessing *Artemisinin-based Combination Antimalarial* related drugs, the WHO *Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies* has been followed.

The two main components of the assessment process are 1) Dossier evaluation, and 2) Manufacturing site inspections. Interested suppliers were requested to submit *Expressions Of Interest (EOI)*. The invitations for submitting Expressions of Interest were published in June 2002 and March 2003. Product dossiers, containing *product data and information for innovator and generic products* were requested for a thorough evaluation. The dossiers were evaluated in accordance with the requirements for the evaluation of Multisource products. (See reference below).

Other criteria taken into account in the assessment process include:

- . • Valid regulatory approval to manufacture
- . • Regulatory or other approval of the product in accordance with national requirements
- . • Product manufactured in compliance with GMP as certified by the national regulatory authority and/or certified GMP inspectors
- . • Product certificate exists in accordance with the WHO certification scheme on the quality of pharmaceutical products moving in international commerce
- . • Product dossier of acceptable quality submitted and positive outcome of the assessment against the WHO recommended standards referred to below.
- . • Positive outcome of the inspection of the manufacturing site performed by inspectors appointed by WHO

In this voluntary assessment process, interested manufacturers were requested to submit product dossiers for various dosage forms and strengths of the products in the categories listed below.

- . • Artesunate (oral preparations)
- . • Dihydroartemisinin (tablets, capsules, paediatric granules, suppositories)
- . • Artemether (oral preparations)
- . • Artemether (intramuscular preparations)
- . • Artemether + lumefantrine (oral preparations)
- . • Artesunate (injection for IV and IM)
- . • Artemotil (injectable forms)

- . • Artesunate + mefloquine (oral preparations)
- . • Artesunate + amodiaquine (oral preparations)
- . • Artesunate + sulphadoxine/pyrimethamine (oral preparations)

### 1. Dossier evaluation.

Dossiers were thoroughly evaluated for compliance with WHO recommendations and guidelines regarding the assessment of Multisource products (*"Marketing Authorization of Pharmaceutical Products with special Reference to Multisource (Generic) Products: a Manual for a Drug Regulatory Authority, WHO/DMP/RGS/98.5*) and bio-equivalence data (*Annex 9, WHO Technical Report Series No 863*), and ICH guidelines where appropriate to complement the aforesaid WHO recommendations and guidelines.

Each product dossier was evaluated by a team of evaluators. Suppliers were informed of the outcome of the evaluation and were given the opportunity to submit additional data and information requested.

Some dossiers have now been fully evaluated and all the required data and information have been submitted. The product that was found to comply with the standards referred to above, has been included in the list.

Several suppliers are currently still generating additional data and information on their products as part of the assessment process. In addition, new products may be submitted to WHO for evaluation. If and when products will be found to meet the specified standards, they will be added to the list.

### 2. Inspections

In regard of products included in the list, inspections have been performed at the manufacturing sites (excluding those manufacturing sites that were recently inspected by regulatory authorities such as members from the Pharmaceutical Inspection Co-operation Scheme (PIC/S), or regulatory authorities with equivalent quality systems. Manufacturers are inspected to assess compliance with Good Manufacturing Practices (GMP) as recommended by the World Health Organization (*Quality Assurance of Pharmaceuticals. A compendium of guidelines and related materials. Volume 2. Good Manufacturing Practices and Inspection*).

The inspections are performed by teams of inspectors. The teams consist of a WHO appointed lead inspector (from countries that are members of the Pharmaceutical Inspection Co-operation Scheme, (PIC/S)), a World Health Organization (WHO) representative from the Medicines Policy and Standards (PSM) , Quality Assurance and Safety: Medicines (QSM) team in WHO, and an inspector(s) from the National Drug Regulatory Authority Inspectorate of the country in which the manufacturing site is located.

The inspection of the manufacturing site includes an in-depth evaluation to assess compliance with GMP. Specific focus is also placed on the manufacturing process of the antimalarial products concerned. Detailed inspection reports, listing all the observations and non-compliances have been drafted and were communicated to manufacturers after each inspection. Where deemed necessary, manufacturers have been required to implement corrective action to address deficiencies, before their product was included in the list.

### **Outcome of the prequalification**

Only products and manufacturing sites found by the evaluators and inspectors to meet the recommendations as stipulated in the WHO guidelines referred to above are and will be included in the list of suppliers whose evaluated products are recommended by WHO as being acceptable in principle for procurement by UN Agencies. (See Table 1)

### **Future of the Programme**

In view of the worldwide focus and importance of the treatment of Malaria, and to facilitate the access to Artemisinin-based Combination Antimalarial drugs of acceptable quality, the programme will continue to evaluate additional product data and information and inspect manufacturing sites. As these meet the specified standards, they will be added to the list.

The list will be reviewed and updated at regular intervals. Products and manufacturing sites included in the list will be re-assessed at regular intervals. Products and manufacturing sites will be removed from the list, if as a result of a re-assessment, it is found that they no longer comply with the specified standards.

**General Notes:**

1. *This list will be updated regularly. Other products are being and will be evaluated and will be added to the list as the data become available, the sites are inspected, and the product and manufacturing sites are found to meet the recommendations and standards as specified in the WHO documentation mentioned above.*
2. *This list indicates the products found to be acceptable in principle, as manufactured at the specified manufacturing sites.*
3. *The UN organization intending to use this list to procure products may wish to ensure that only products from the manufacturing sites mentioned in this list will be supplied by the supplier (same formula, manufacturing methods, manufacturing site as in the dossier provided for this project).*
4. *This list does not constitute any guarantee for the procurement of the products from the suppliers mentioned.*
5. *The fact that certain products and suppliers are not included in the list does not furthermore mean that if evaluated and tested, they could not be found to comply with the above-mentioned standards.*
6. *This list may not be used by manufacturers and suppliers for commercial or promotional purposes.*
7. *This list is not an exhaustive list of pharmaceutical products used in the treatment of Malaria. It reflects those products for which data have been submitted and evaluated as a result of the Prequalification Programme: Priority Essential medicines, by interested suppliers which voluntarily participated in the assessment programme. There is furthermore no guarantee that the products included in the list and found to comply with the above-mentioned standards will continue to meet those standards.*
8. *This list reflects those products (manufactured at the specified manufacturing sites) with respect to which the product data and information submitted were found to meet the norms and standards recommended by WHO. The manufacturing sites listed are those which have subsequently, as part of the procedure, been found to meet the norms and standards recommended by WHO at the time of inspection to assess compliance with Good Manufacturing Practice for the products listed. Inclusion in the list does not, however, imply any approval by WHO of the products and manufacturing sites in question (which is the sole prerogative of national authorities).*

9. *It is recommended that prior to procurement, UN organizations familiarize themselves with aspects such as quantification and patents of the products in question as well as other related matters.*
10. *Assessment of additional products and manufacturing sites will be carried out at regular intervals.*

**Disclaimer:**

Inclusion in the list does not constitute an endorsement, or warranty of the fitness, of any product for a particular purpose, including in regard of its safety and/or efficacy in the treatment of Malaria. WHO does not furthermore warrant or represent that: 1) the list is complete or error free; and/or that 2) the products and manufacturing sites which have been found to meet the standards recommended by WHO, will continue to do so; and/or that 3) the products listed have obtained regulatory approval for use in the treatment of Malaria (or any other disease) in every country of the world, or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws. In addition, WHO wishes to alert procuring UN Agencies that the improper storage, handling and transportation of drugs may affect their quality, efficacy and safety. WHO disclaims any and all liability and responsibility for any injury, death, loss, damage or other prejudice of any kind whatsoever that may arise as a result of, or in connection with the procurement, distribution and use of any product included in the list.

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