Recommended Comparator Products: Anti-malarial Medicines

Comparator products should be purchased from a well-regulated market with stringent regulatory authority [*].

Invited medicinal products (refer to EOI for more information e.g. requirements for scoring)	Recommended comparator product (Strength, Manufacturer)
Artemisinin-based oral combination products	
Artemether/Lumefantrine tablet, 20 mg/120 mg 40 mg/240 mg 60 mg/360 mg 80 mg/480 mg	Riamet or Coartem (Artemether/Lumefantrine 20 mg/120 mg tablet, Novartis)
Artesunate/Amodiaquine tablet, 25 mg/67.5 mg 50 mg/135 mg 100 mg/270 mg	Coarsucam or Artesunate/Amodiaquine Winthrop tablet (Artesunate/Amodiaquine 25 mg/67.5 mg tablet, Artesunate/Amodiaquine 50 mg/135 mg tablet, Artesunate/Amodiaquine 100 mg/270 mg tablet, Sanofi-Aventis)
Amodiaquine + Sulphadoxine/Pyrimethamine tablet, 75 mg + 250mg/12.5 mg 150 mg + 500 mg/25 mg (co-packaged) or 76.5 mg + 250 mg/12.5 mg 153 mg + 500 mg/25 mg (co-packaged)	*Please see footnote 1 below*
Artesunate/Mefloquine tablet, 25 mg/50 mg 100 mg/200 mg	*Please see footnote 1 below for artesunate* Lariam (Mefloquine 250 mg tablet, Roche) or Mefloquine hydrochloride 250 mg tablet (Barr Laboratories Inc, US[2])
Artesunate/Pyronaridine tetraphosphate granules, 20 mg/60 mg Artesunate/Pyronaridine tetraphosphate tablet, 60 mg/180 mg	Artesunate/Pyronaridine tetraphosphate 20 mg/60 mg granules (Shin Poong Pharmaceutical Co Ltd, Kyunggi-Do, Republic of Korea) Artesunate/Pyronaridine tetraphosphate 60 mg/180 mg tablet (Shin Poong Pharmaceutical Co Ltd, Kyunggi-Do, Republic of Korea)
Dihydro-artemisinin/Piperaquine phosphate tablet, 20 mg/160 mg 30 mg/240 mg 40 mg/320 mg 60 mg/480 mg 80 mg/640 mg	Eurartesim (dihydro-artemisinin/piperaquine phosphate 20/160 mg tablet, dihydro-artemisinin/piperaquine phosphate 40/320 mg tablet, Alfasigma S.p.A)

Other antimalarial medicines	
Artesunate, 25 mg, 50 mg and 100 mg tablet[3]	*Please see footnote 1 below*
Artesunate, 30 mg, 60 mg and 120 mg powder for solution for injection (vial)	Artesun (artesunate, 60 mg powder for solution for injection, Guilin Pharmaceutical Co Ltd) Artesunate (110 mg/vial, solution for i.v. injection, Amivas)
Artesunate 50 mg, 100 mg and 200 mg suppositories	Artesunate Rectocaps 100 mg (Cipla Ltd)[1] Artecap 100 mg (Strides Pharma) [1]
Mefloquine, 250 mg tablet	Lariam (Mefloquine 250 mg tablet, Roche) Mefloquine hydrochloride 250 mg tablet (Barr Laboratories Inc, US[2])
Primaquine, 2.5, 5, 7.5 and 15 mg (as base) tablet	Primaquine 15 mg tablet (Sanofi-Aventis, US[2])
Sulphadoxine/Pyrimethamine tablet, 250 mg/12.5 mg 500 mg/25 mg	Fansidar (sulphadoxine/pyrimethamine 500 mg/25 mg tablet, Ascendis Pharma, South Africa[4]) *For alternative comparator products, please see footnote 1 below*
Tafenoquine 150 mg tablet Tafenoquine 50 mg dispersible tablet	Krintafel 150 mg tablet, GSK Kozenis 150 mg tablet, GSK Kozenis 50 mg dispersible tablet, GSK

[1] Consult the PQ Team regarding the comparator product.
[2] The recommended comparator product is approved by USFDA; the comparator product should be obtained from the US market.
[3] Artesunate tablets are to be used only in co-packaged products with Mefloquine.
[4] The comparator product should be obtained from the South African market.

* A regulatory authority that is:

a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

Obtaining Comparator

Comparator products should be purchased from a well-regulated market with stringent regulatory authority. If the recommended comparator cannot be located for purchase from the market of one of the identified countries, the applicant should consult with WHO regarding the sourcing of an acceptable comparator product.

Information Requirements

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme.

Dose Equivalence

In case the invited product has a different strength compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation between similar doses may be applied by dose normalisation.

Fixed-dose Combination Products

The bioequivalence of fixed-dose combination (FDC) product should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product as listed above. In cases where a FDC comparator product is not listed above, individual component products administered in loose combination should be used as a comparator. The principles of dose normalization as mentioned above are applicable.

Suitability of a comparator product for BCS-based biowaiver applications

Recommendation of an API for BCS-based biowaivers is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3) — see the Biowaiver guidance documents on the WHO Prequalification website. It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification website is indeed suitable for a BCS based-biowaiver application before product development.

Rapidly dissolving (or very rapidly dissolving) properties of a product are not required for in vivo bioequivalence studies. Accordingly, although a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.