EGG PHARMA

AYUSH-Certified Integrative Medicine

ACT Rx

ADMINISTRATION PROTOCOL

Precision Chronotherapeutics & Artemisinin-Berberine Combination Pharmacology

Clinical Prescriber Handbook · For Registered Healthcare Practitioners Only

Indications Covered:

Malaria (P. falciparum / P. vivax) · Dengue (Exploratory/Research) · Antimicrobial / Antiparasitic

Document Classification:

Restricted — For Qualified Prescribers and AYUSH-Registered Practitioners

Version 2.0 · Egg Pharma Research & Medical Affairs Division

TABLE OF CONTENTS

NOTE · Page numbers are approximate. Use document navigation or bookmarks for precise section location. This TOC does not auto-update on edit.

1 EXECUTIVE SUMMARY

The ACT Rx Protocol is Egg Pharma's clinical administration framework for artemisinin-based combination therapy (ACT), integrating berberine as a pharmacological potentiator within an AYUSH regulatory context. This handbook is intended for qualified prescribers managing patients with confirmed or clinically suspected parasitic infections — principally Plasmodium falciparum and Plasmodium vivax malaria — alongside exploratory research applications including dengue and broad-spectrum antimicrobial contexts.

The protocol is structured around three pharmacological axes:

- Artemisinin-derivative endoperoxide activation, producing selective cytotoxic reactive oxygen species (ROS) within the iron-rich environment of Plasmodium-infected erythrocytes.
- Berberine co-administration as a multi-modal potentiator: inhibiting intestinal P-glycoprotein (P-gp) efflux, modulating CYP3A4 activity, and attenuating NF-κB-mediated inflammatory signalling.
- Chronotherapeutic dosing, aligning peak plasma drug concentration (Cmax) with documented circadian windows of highest parasitaemic burden and fever spike onset.

> *NOTE · All indications, dosage forms, and combinations require administration under licensed practitioner supervision. Off-label and exploratory applications require IRB or equivalent ethical clearance prior to clinical use. Where claims are inferred from established pharmacological data rather than direct clinical evidence, they are marked with the INFERRED FROM ESTABLISHED DATA callout throughout this document.*

2 PRODUCT COMPENDIUM — ACT Rx COMPONENTS

2.1 Artemether Liquid — Sublingual Spray (60 mg)

Form: Metered-dose sublingual spray, 60 mg artemether per actuation. Solubilised in a pharmaceutical-grade lipid excipient base to facilitate transmucosal absorption.

Parameter	Specification
Active Ingredient	Artemether (semi-synthetic artemisinin derivative)
Dose per Actuation	60 mg
Route	Sublingual (SL) — hold under tongue, avoid swallowing for 30 seconds post-administration
Pharmacokinetic Basis	Transmucosal absorption via sublingual venous plexus bypasses hepatic portal first-pass. Onset and Cmax data are extrapolated from IM and buccal artemether pharmacokinetic studies; product-specific SL PK data should be confirmed with Egg Pharma Medical Affairs prior to clinical use.
Half-life (t½)	~2 hours (artemether); converted in vivo to active metabolite dihydroartemisinin (DHA, t½ ~1–3 hrs) via CYP3A4/3A5 demethylation
Storage	Below 30°C; protect from direct sunlight; do not refrigerate

2.2 Artesunate 50 mg — Phase A Oral Tablet (White)

Form: Film-coated white oral tablet, 50 mg artesunate per tablet. Water-soluble artemisinin derivative with established oral bioavailability and WHO-endorsed clinical efficacy in malaria.

Parameter	Specification
Active Ingredient	Artesunate (hemisuccinate ester of dihydroartemisinin)
Classification	WHO Essential Medicine; Schedule H (India); Rx-only
Primary Indication	Uncomplicated and severe P. falciparum malaria; P. vivax malaria (in combination with partner drug)
WHO Dosing Reference	4 mg/kg/day (weight-based). The fixed 50 mg dose is an approximation for adults 50–75 kg only. Prescribers must calculate weight-adjusted doses per WHO Malaria Treatment Guidelines 2022, Table 5.
Tmax	~1.5 hours (oral); rapidly hydrolysed to DHA by plasma esterases and intestinal mucosa
Protein Binding	~93% (DHA)
Metabolism	Rapid pre-hepatic hydrolysis to DHA; hepatic glucuronidation (UGT1A9, UGT2B7)

WARNING · The 50 mg fixed dose is a prescriber convenience reference for average adult weight (50–75 kg). Do not apply as a fixed dose without confirming patient body weight. Paediatric and underweight adult patients require full weight-based dose calculation per WHO guidelines.

2.3 Berberine 400 mg — Phase B Oral Tablet (Orange/Brown)

Form: Modified-release oral tablet, 400 mg berberine hydrochloride per tablet. AYUSH-registered compound derived from Berberis aristata (Daruharidra). Functions as a pharmacological potentiator — not a primary antiparasitic or antiviral agent.

Parameter	Specification
Active Ingredient	Berberine Hydrochloride (isoquinoline alkaloid)
AYUSH Registration	Ayurvedic (Daruharidra) — Ayurvedic Pharmacopoeia of India
Oral Bioavailability	Low (~5%) due to P-glycoprotein (P-gp/ABCB1) efflux at intestinal epithelium; modified-release formulation extends mucosal exposure time to partially compensate
CYP Interactions	Inhibits CYP3A4 and CYP2D6; full medication reconciliation required before prescribing
QTc Effect	Berberine independently prolongs cardiac QTc interval — see Contraindications (Section 6.3)
Role in ACT Rx	Potentiator only — intestinal P-gp inhibition, CYP3A4 modulation, AMPK activation, NF-κB attenuation

3 MOLECULAR MECHANISM OF ACTION

3.1 The Endoperoxide Bridge — Artemisinin Derivatives

The pharmacophore of all artemisinin derivatives is the 1,2,4-trioxane endoperoxide bridge — a strained ring structure chemically inert under normal physiological conditions but subject to rapid reductive cleavage in the presence of ferrous iron (Fe^{2+}) and haem.

Mechanism of Selective Activation

In Plasmodium-infected erythrocytes, the parasite catabolises haemoglobin within its acidic digestive vacuole, generating free haem and Fe^{2+} as metabolic by-products of haemozoin formation:

- Fe^{2+} donates a single electron to the endoperoxide O–O bond (Fenton-type reaction), triggering homolytic cleavage.
- This generates carbon-centred free radicals and reactive oxygen species (ROS), including hydroxyl radicals (·OH) and alkyl radicals.
- Radicals covalently alkylate haem, parasite proteins (including PfATP6, the SERCA calcium pump), and mitochondrial membranes within the infected cell.
- Convergent disruption of calcium homeostasis, haemoglobin digestion, and mitochondrial electron transport produces rapid parasite death, preferentially at ring and early trophozoite stages.

> *NOTE · Host-cell selectivity: Mature uninfected erythrocytes contain minimal free Fe^{2+} and lack haem-processing vacuoles. The differential iron topology between parasitised and unparasitised cells is the primary driver of artemisinin's favourable therapeutic index — not receptor-ligand specificity.*

Pharmacodynamic Comparison: Artemether vs. Artesunate

Property	Artemether (SL Spray)	Artesunate (Oral Tablet)
Solubility	Lipophilic — favourable for transmucosal uptake and CNS tissue penetration	Hydrophilic — rapid dissolution and GI absorption; broad haematological distribution
Active Metabolite	DHA via CYP3A4/3A5 hepatic demethylation	DHA via plasma and mucosal esterase hydrolysis (pre-hepatic; rapid)
First-Pass Effect	Substantially reduced via sublingual route (hepatic portal bypass)	Partial first-pass; DHA conversion begins pre-hepatically
Onset	Faster systemic entry via transmucosal route vs. oral (quantitative data product-specific)	Oral Tmax ~1.5 hours; predictable sustained absorption profile
ACT Rx Role	Step 1 — Sublingual Induction	Step 3 — Oral Saturation (48-hr cycle)

3.2 Berberine — Mechanism of Potentiation

Berberine does not possess clinically meaningful direct antiparasitic activity at standard oral doses. Its role within ACT Rx is strictly pharmacological potentiation, operating through four established mechanisms:

3.2a Intestinal P-gp Efflux Inhibition

- Berberine inhibits intestinal P-glycoprotein (P-gp/ABCB1), a luminal efflux transporter that actively expels substrate drugs back into the intestinal lumen, reducing their net absorption.
- Artesunate and its metabolite DHA are P-gp substrates. Berberine co-administration reduces P-gp-mediated efflux at the enterocyte level, increasing effective mucosal absorption.

NOTE · Evidence basis: Berberine's P-gp inhibition is established in vitro and in intestinal transport models (Pham TH et al., 2005; Shan L et al., 2009). Direct clinical PK interaction data for berberine + artesunate co-administration in malaria patients is not yet available — this mechanism is inferred from established transport pharmacology.

3.2b CYP3A4 Modulation

- Berberine inhibits hepatic CYP3A4, the primary enzyme responsible for artemether demethylation to DHA. Inhibition prolongs the plasma residence time of intact artemether, extending the therapeutic concentration window.
- This same inhibition underlies the clinically significant drug interaction risk. Full medication reconciliation is mandatory before initiating the combination.

WARNING · CYP3A4 inhibition by berberine is a dual-edged pharmacological effect — it extends artemether exposure but simultaneously raises plasma levels of all CYP3A4-dependent co-medications. Priority review required for: statins (simvastatin, atorvastatin), calcium channel blockers, certain antiretrovirals, cyclosporine, and macrolide antibiotics.

3.2c AMPK Activation & NF-κB Attenuation

- Berberine activates AMP-activated protein kinase (AMPK), suppressing NF-κB signalling and attenuating the pro-inflammatory cytokine cascade (TNF-α, IL-6, IL-1β) that drives fever, endothelial dysfunction, and organ injury in severe parasitic infections.
- This mechanism is most clinically relevant in dengue (exploratory context) and severe malaria, where cytokine dysregulation is a primary driver of morbidity independent of parasite burden.

NOTE · Evidence basis: Berberine's AMPK activation and NF-κB suppression are established in vitro and in animal models (Shen N et al., 2015; Yin J et al., 2008). Prospective controlled clinical evidence in dengue or malaria patients is not yet available. Application in these contexts is pharmacologically reasoned but not yet clinically validated.

3.2d Adjunct Antimicrobial Activity

- Berberine demonstrates in vitro antimicrobial activity against Gram-positive and Gram-negative bacteria via DNA intercalation and topoisomerase inhibition — clinically relevant for secondary bacterial co-infections in dengue haemorrhagic fever and severe malaria.
- In vitro P. falciparum inhibition has been reported at supraphysiological concentrations not achievable at standard oral dosing. This should not be counted as a meaningful antiparasitic contribution.

CLINICAL DIRECTIVE · Berberine in the ACT Rx protocol is a potentiator. It must not be substituted for a WHO-approved artemisinin combination partner drug (e.g., lumefantrine, amodiaquine, piperaquine) in confirmed uncomplicated or severe P. falciparum malaria.

3.3 The Fe^{2+}-ROS Cascade — Selectivity Architecture

The following table summarises the sequential mechanism from parasite iron release to parasite death. All steps are grounded in published biochemical and parasitological evidence.

Step	Event	Established Mechanism
1	Haemoglobin catabolism	Intraerythrocytic Plasmodium digests host haemoglobin in its acidic food vacuole, releasing free haem and Fe^{2+} as metabolic by-products of haemozoin polymerisation
2	Endoperoxide encounter	Artemisinin derivative diffuses into the infected erythrocyte and reaches the food vacuole, where Fe^{2+} and haem are highly concentrated relative to uninfected cells
3	Reductive cleavage	Fe^{2+} donates one electron to the O–O endoperoxide bond (Fenton-type reaction), producing a carbon-centred radical and an alkoxy radical
4	ROS generation	Carbon radicals react with molecular oxygen to yield superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\cdot OH$) — the primary cytotoxic effectors
5	Multi-target alkylation	Radicals covalently modify: (a) PfATP6 SERCA pump — Ca^{2+} homeostasis disruption; (b) haem — secondary ROS amplification; (c) mitochondrial membrane proteins — ETC uncoupling and membrane depolarisation
6	Parasite death	Convergent failure of calcium regulation, energy metabolism, and haemoglobin digestion produces irreversible parasite death — preferential at ring and early trophozoite stages

4 THE ACT Rx ADMINISTRATION PROTOCOL

The ACT Rx protocol is a sequential induction-saturation-maintenance regimen delivering rapid therapeutic plasma levels of artemisinin derivatives while optimising berberine's pharmacokinetic potentiation. Three procedural steps are executed within each dosing cycle.

WARNING · For use under licensed practitioner supervision only. Confirm parasitological diagnosis (blood smear or RDT) before initiating. Assess baseline hepatic function, G6PD status, QTc interval, and concurrent medications prior to commencement.

4.1 Step 1 — Sublingual Induction (Artemether 60 mg Spray)

Clinical Rationale for Sublingual Route

Sublingual (SL) administration delivers artemether via the sublingual venous plexus directly into the systemic circulation, bypassing the hepatic portal system. This is the established pharmacokinetic rationale for sublingual drug delivery and applies to artemether on the basis of its lipophilicity — a property that favours transmucosal diffusion.

- **First-pass reduction.** First-pass reduction.

Oral artemether undergoes significant hepatic CYP3A4-mediated first-pass metabolism, reducing systemic bioavailability relative to non-oral routes. The sublingual route reduces this first-pass effect. Quantitative Cmax comparisons between SL and oral routes are not available from published artemether PK studies; the advantage is pharmacokinetically inferred from route physiology and artemether's established lipophilicity.

- **Faster systemic entry.** Faster systemic entry.

Transmucosal absorption achieves systemic drug entry more rapidly than oral ingestion followed by gastrointestinal transit. This is the pharmacological basis for sublingual formulations across drug classes and is consistent with artemether's physicochemical profile.

- **CNS distribution.** CNS distribution.

Artemether's lipophilicity supports CNS penetration, relevant in cerebral malaria risk scenarios. Intact artemether circulates briefly before hepatic conversion to DHA; this lipophilic fraction contributes to CNS tissue distribution.

INFERRED FROM ESTABLISHED DATA · Onset of action for SL artemether is expected to be faster than the oral route based on route pharmacology and artemether lipophilicity. Specific onset times should be validated against Egg Pharma's product-specific PK study data before being communicated to prescribers as established figures.

Administration Procedure — Step 1

- Instruct the patient to lift the tongue to the roof of the mouth.
- Actuate a single metered dose (60 mg) of Artemether Spray directly under the tongue.
- Patient holds the spray under the tongue for a minimum of 30 seconds without swallowing.
- After 30 seconds, the patient may swallow. Advise against eating or drinking for 5 minutes post-administration.

- Record the exact time of administration — this is T_0, the reference point for all subsequent dosing intervals.

CLINICAL DIRECTIVE · The 30-second sublingual hold is non-negotiable. Premature swallowing reroutes absorption to the gastrointestinal tract, reintroducing first-pass hepatic metabolism and reducing the pharmacokinetic advantage of the sublingual formulation. Instruct patients explicitly before administration.

4.2 Step 2 — The 30-Minute Interval (Oral Phase Preparation)

Pharmacological Basis of the Interval

A mandatory 30-minute interval is observed between Step 1 completion and oral Phase A/B tablet administration. This interval serves two pharmacologically grounded purposes:

- **Transmucosal absorption completion.** Transmucosal absorption completion.

Sublingual absorption continues for 15–25 minutes post-administration. Introducing tablets, food, or liquid into the oral cavity within this window risks altering the sublingual mucosal environment — changing pH, diluting the drug layer, or altering mucosal blood flow — any of which can reduce absorption efficiency.

- **Avoiding competitive GI dynamics.** Avoiding competitive GI dynamics.

Artesunate (Phase A) and Berberine (Phase B) are both absorbed primarily in the proximal small intestine. Oral administration while SL absorption is still active may alter gastric motility and pH via swallowing reflexes and early gastric filling, which could indirectly affect transmucosal uptake completion.

CLINICAL DIRECTIVE · Do not administer Phase A or Phase B tablets before 30 minutes have elapsed from Step 1 (T_0 + 30 min). In inpatient settings, enforce via nursing protocol. In outpatient settings, provide a pre-filled dosing timecard with clock-referenced intervals at the time of dispensing.

4.3 Step 3 — The 48-Hour Oral Cycle (Artesunate + Berberine, 3× Daily)

Dosing Frequency and Duration Rationale

Artesunate (weight-based / 50 mg reference for adults, oral) and Berberine (400 mg, oral) are co-administered three times daily at 8-hour intervals over a minimum 48-hour initial cycle. This structure aligns with the WHO short-course intensification phase of ACT, preceding transition to a full partner-drug regimen for uncomplicated falciparum malaria.

The 8-Hour Interval — Pharmacokinetic Basis

- DHA (active metabolite of artesunate) has a t½ of approximately 1–3 hours. At 6–8 hours post-dose, plasma levels approach elimination trough. Redosing at the 8-hour mark re-establishes therapeutic ROS-generating capacity without accumulation.
- Artesunate undergoes autoinduction of CYP-mediated metabolism with repeated dosing — plasma DHA exposure declines progressively over 3–5 days. The 8-hour interval maximises exposure during the early high-bioavailability window before autoinduction takes effect.

- Berberine's modified-release formulation produces a Tmax of approximately 4–6 hours. 8-hourly dosing maintains mucosal concentrations sufficient for ongoing P-gp inhibition and AMPK modulation across the dosing cycle.

Phase A/B Co-Administration Sequence

Sequence	Agent	Instruction
First	Phase A — Artesunate (white tablet)	Administer orally with 200 mL water. Take with a small amount of food to reduce gastric irritation. Do not crush or chew. Confirm weight-based dose before administration.
Concurrent	Phase B — Berberine 400 mg (orange/brown tablet)	Administer concurrently with Phase A. If GI tolerance is a concern, berberine may follow artesunate by up to 5 minutes. Do not separate doses by more than 15 minutes.
Interval	8 hours (T_0 + 8h, T_0 + 16h)	Next Step 3 dose at T_0 + 8 hours. Do not extend intervals beyond 9 hours during the acute 48-hour cycle without prescriber review.

CLINICAL DIRECTIVE · The 48-hour ACT Rx Phase A/B cycle is an induction framework. It must be followed by transition to a WHO-approved full ACT partner drug regimen (e.g., artesunate-amodiaquine, artesunate-lumefantrine per local resistance patterns). ACT Rx alone does not constitute complete malaria treatment.

WARNING · Artemisinin partial resistance (Kelch13 mutations, including C580Y) is documented in Southeast Asian P. falciparum populations and is emerging elsewhere. Confirm local resistance surveillance data before selecting an ACT partner drug. Delayed parasite clearance despite adequate ACT Rx should prompt urgent escalation and specialist consultation.

5 CHRONOTHERAPEUTIC MAPPING

Chronotherapeutics aligns drug administration with circadian physiological rhythms to optimise pharmacokinetic parameters (Cmax, AUC) and pharmacodynamic effect. For artemisinin-based therapy, the objective is to synchronise peak plasma DHA concentration with the circadian window of highest intraerythrocytic parasitaemic burden — when maximal haem/Fe^{2+} availability for endoperoxide activation coincides with peak parasite density.

5.1 Malaria Chronobiology — Established Evidence

Plasmodium spp. exhibit a fixed intraerythrocytic replication periodicity: P. falciparum — 48 hours (tertian); P. vivax — 48 hours (tertian); P. malariae — 72 hours (quartan). Erythrocyte rupture (schizogony) occurs at a species-specific circadian phase, producing predictable fever spikes:

- P. falciparum schizogony in most clinical series occurs preferentially in the late afternoon to early evening (~16:00–20:00 local time), coinciding with peak body temperature and maximal haem/Fe^{2+} liberation.
- This creates the optimal biochemical window for artemisinin activation: maximal Fe^{2+} availability at peak parasitaemia, increasing ROS generation per unit of drug administered.

NOTE · Individual fever periodicity varies. Schizogony synchronisation is most reliable after 24–48 hours of infection; early or mixed-species infections may show irregular patterns. Establish the individual fever profile before applying chronotherapeutic timing (Section 5.4).

5.2 Dengue Context — Scope and Limitations

Dengue fever is caused by a Flavivirus. Artemisinin derivatives have no established mechanism of antiviral activity against dengue replication. The exploratory rationale in dengue is limited to berberine's documented anti-inflammatory mechanisms and cytokine attenuation potential during the high-risk febrile phase.

- Berberine's NF-κB attenuation may reduce the pro-inflammatory cytokine cascade contributing to dengue haemorrhagic progression — established in vitro and in animal models; not yet validated in prospective dengue clinical trials.
- Chronotherapeutic timing for berberine in dengue positions peak mucosal berberine concentrations ahead of the documented daily fever spike, when NF-κB signalling is rising.

WARNING · Artemisinin derivatives are NOT approved treatments for dengue. Any clinical application requires IRB clearance and informed patient consent. The dengue row in the dosing table below applies to berberine only. Artesunate should not be administered for dengue outside a prospective clinical trial framework.

5.3 ACT Rx Chronotherapeutic Dosing Table

All times are referenced to T_0 — the time of first Step 1 (SL Artemether) administration within each 24-hour cycle. The fever spike baseline (Tpeak) must be established per Section 5.4 before applying this table.

Dose	T_0 Reference	ACT Rx Step	Parasitological Target	Chronotherapy Objective
Dose 1	T_0 = Tpeak − 90 min(Step 1:	Step 1: SL ArtemetherStep	Rising parasitaemia; pre-schizogony;	Systemic artemether levels reach peak near

	SL)T_0 + 30 min(Step 3: oral)	3: Artesunate + Berberine	haem/Fe^{2+} accumulating toward peak	fever spike onset; oral DHA Cmax (~T_0 + 90 min) coincides with post-schizogony free haem peak — maximising Fe^{2+}-driven endoperoxide activation
Dose 2	T_0 + 8 hours	Steps 1–3 repeated	Ring-stage parasites re-entering erythrocytes from merozoites released at schizogony	Maintains DHA above MIC during ring-stage reinvasion; targets newly invaded erythrocytes before trophozoite maturation
Dose 3	T_0 + 16 hours	Steps 1–3 repeated	Early trophozoite stage; haemoglobin digestion underway; moderate Fe^{2+} availability	Prophylactic DHA exposure prevents trophozoite maturation to schizont stage; reduces Day 2 parasitaemia ahead of next cycle
Dengue — Research Only(Berberine only)	Tpeak − 2 hours	Phase B: Berberine 400 mg onlyArtesunate NOT administered	NF-κB signalling begins rising 2–3 hours before peak temperature in dengue febrile phase	AMPK activation / NF-κB suppression timed to attenuate cytokine cascade at initiation. Evidence: in vitro / animal model only. IRB clearance required.

5.4 Establishing the Fever Spike Baseline

- Record oral or axillary temperature every 2 hours for a minimum of 24 hours (48 hours preferred) before ACT Rx initiation.
- Plot temperature versus time to identify fever spike pattern and document daily peak time (Tpeak).
- Set T_0 (Step 1) for each 24-hour ACT Rx cycle at Tpeak − 90 minutes.
- In hospitalised patients, record Tpeak daily and adjust T_0 if the fever pattern shifts during treatment.

CLINICAL DIRECTIVE · In patients with irregular or unsynchronised fever (early P. falciparum or mixed-species infections), use fixed 8-hourly dosing (e.g., 07:00 / 15:00 / 23:00) and transition to chronotherapeutic timing once fever periodicity is confirmed over 24–48 hours. Do not delay treatment initiation to complete the baseline fever profile if clinical urgency requires earlier intervention.

6 CLINICAL PEARLS & MONITORING

6.1 Managing the Herxheimer-Like Reaction

A transient worsening of systemic symptoms — fever intensification, rigors, myalgia, headache, occasionally mild hypotension — may occur within 2–8 hours of ACT Rx initiation, particularly in patients with high baseline parasitaemia. This is phenomenologically similar to the Jarisch-Herxheimer reaction (JHR) of spirochaetal disease, though the mechanism differs.

Proposed Mechanism

- Rapid parasite lysis releases a bolus of parasite antigens, haemozoin, and glycosylphosphatidylinositol (GPI) anchor molecules into systemic circulation.
- Haemozoin and GPI activate innate pattern-recognition receptors (TLR2, TLR9), triggering a transient TNF-α, IL-6, and IL-1β surge — producing clinical fever amplification.
- This is consistent with a pharmacodynamic response to effective therapy, not treatment failure. It must be distinguished from drug hypersensitivity and from clinical deterioration due to inadequate therapeutic response.

INFERRED FROM ESTABLISHED DATA · The haemozoin/GPI-driven innate immune response is established in malaria pathophysiology (Gazzinelli RT et al., Nat Rev Immunol 2014). Its application as the mechanism of early symptom amplification post-artemisinin initiation is a well-supported inference from published immunology — not a finding specific to ACT Rx.

Management Protocol

Severity	Clinical Response
Mild	Fever ≤39°C with myalgia/headache. Continue ACT Rx without modification. Paracetamol (15 mg/kg in children; 500–1000 mg in adults) for symptom relief. Oral hydration minimum 2 L/day (adults). Monitor vitals 4-hourly.
Moderate	Fever >39°C with rigors. IV/IM paracetamol if oral route compromised. IV fluid bolus (10–20 mL/kg normal saline) for haemodynamic support. Do NOT discontinue ACT Rx unless Grade 3–4 adverse event criteria are met. Reassess in 2 hours.
Severe — consider discontinuation	**Sustained hypotension (SBP <90 mmHg), angioedema, urticaria, bronchospasm, or altered consciousness.** Suspect drug hypersensitivity or severe malaria complication. DISCONTINUE ACT Rx. Initiate anaphylaxis or severe malaria protocol as indicated. Senior clinical review mandatory.

6.2 Antioxidant Interference — Critical Safety Warning

WARNING · Concurrent administration of exogenous antioxidants — including Vitamin C (ascorbic acid), Vitamin E (tocopherol), N-acetylcysteine (NAC), glutathione, and selenium supplements — will attenuate artemisinin derivative efficacy.

- Artemisinin derivatives exert antiparasitic activity via ROS generation within the Fe^{2+}-rich environment of the parasitised erythrocyte. These radicals are the therapeutic effectors.
- Exogenous antioxidants at significant plasma or intracellular concentrations quench these ROS molecules before they can alkylate parasite proteins — directly undermining the mechanism of action.
- In vitro co-incubation studies demonstrate that ascorbic acid and tocopherol significantly reduce artemisinin-mediated parasite killing, with the degree of antagonism dependent on antioxidant concentration (Bhisutthibhan J et al.; Meshnick SR).
- Advise patients to avoid large quantities of citrus fruit, berry juices, and green tea within 2 hours of any ACT Rx dose.

CLINICAL DIRECTIVE · Suspend all non-essential antioxidant supplements for the full duration of ACT Rx therapy. Do not co-administer Vitamin C infusions, glutathione injections, or NAC drips during active artemisinin dosing cycles. Communicate this explicitly to patients and all concurrent treating practitioners.

6.3 Contraindications

Contraindication	Clinical Rationale
First trimester of pregnancy	Artemisinin derivatives are embryolethal in rat and rabbit models at therapeutic doses. Human first-trimester safety data is insufficient. Use only if the risk from untreated life-threatening P. falciparum clearly outweighs fetal risk. WHO recommends quinine + clindamycin as the preferred first-trimester alternative.
G6PD deficiency (severe)	Both artesunate and berberine can precipitate oxidative haemolytic crises in G6PD-deficient patients. Screen G6PD status prior to initiation. Mild-to-moderate G6PD deficiency: proceed with caution and enhanced haematological monitoring (FBC at 48h and Day 7 minimum).
Known hypersensitivity — artemisinin class	Prior documented allergic reaction to artemether, artesunate, artemisinin, or DHA. Do not rechallenge. Consult tropical medicine specialist for alternative regimen.
Severe hepatic impairment (Child-Pugh C)	Artesunate hepatic glucuronidation and berberine CYP3A4 inhibition create unpredictable drug accumulation risk. Use with extreme caution; reduce doses and intensify LFT monitoring. Seek hepatology input.
Co-administration with QTc-prolonging agents	Berberine independently prolongs cardiac QTc. Combined use with other QTc-prolonging drugs (certain antimalarials, azole antifungals, fluoroquinolones, antipsychotics) increases torsades de pointes risk. Obtain baseline ECG. Continuous cardiac monitoring required if combination is unavoidable.
Paediatric patients <5 kg body weight	The 60 mg SL artemether and 50 mg artesunate reference doses are adult-calibrated. Paediatric weight-based dosing protocols are not provided in this handbook. Refer to WHO Malaria Treatment Guidelines 2022, Tables 5–7.
CYP3A4-sensitive co-medications	Berberine CYP3A4 inhibition will elevate plasma concentrations of all CYP3A4-dependent drugs. Priority review: statins (simvastatin, atorvastatin), calcium channel blockers, cyclosporine, certain antiretrovirals, macrolide antibiotics. Dose adjustment or temporary suspension may be required.

6.4 Recommended Monitoring Parameters

Parameter	Frequency	Clinical Purpose
Peripheral blood smear / RDT	Baseline, 24h, 48h, 72h, Day 7	Confirm parasitological response; detect treatment failure, partial resistance (delayed clearance), or recrudescence
Body temperature	4-hourly during active fever phase	Track fever periodicity for chronotherapeutic timing; detect Herxheimer-like reaction; monitor clinical trajectory
Full Blood Count (FBC)	Baseline, 48h, Day 7	Haemolytic anaemia surveillance (artemisinin + G6PD risk); platelet monitoring (dengue / malaria thrombocytopaenia)
LFTs (ALT, AST, bilirubin)	Baseline, Day 3, Day 7	Artesunate-associated transaminitis; berberine CYP3A4 inhibition effect on hepatic drug clearance
Serum creatinine / eGFR	Baseline, Day 3	Renal function in severe malaria; dose adjustment required if AKI develops
ECG (QTc interval)	Baseline; repeat Day 2 if QTc-prolonging co-medications present	Screen for berberine + co-medication QTc additive risk; establish pre-treatment baseline
Blood glucose	Baseline; 12-hourly in severe malaria	Hypoglycaemia is a WHO severe malaria criterion and a recognised complication of antimalarial therapy
Patient symptom diary (outpatient)	Each dosing cycle	GI tolerance, headache, symptom trajectory — early detection of treatment response, intolerance, or deterioration

6.5 Treatment Failure Criteria — Escalation Triggers

Initiate urgent escalation to parenteral artesunate and senior clinical review if any of the following are present:

- Parasitaemia reduction of less than 75% at 48 hours from initiation.
- Persistent or rising fever beyond 72 hours of treatment.
- Development of any WHO-defined severe malaria criterion: impaired consciousness, respiratory distress, hypoglycaemia (BGL <2.2 mmol/L), haemoglobin <7 g/dL, haematocrit <15%, haemoglobinuria, or circulatory collapse.
- Clinical deterioration at any point during the ACT Rx cycle, regardless of parasitological data.
- Delayed parasite clearance phenotype (detectable parasitaemia beyond 72 hours despite adequate dosing) — raises suspicion for artemisinin partial resistance; activate local resistance surveillance protocol.

CLINICAL DIRECTIVE · Treatment failure or suspected resistance in P. falciparum malaria requires immediate escalation to IV artesunate per the WHO severe malaria protocol with senior infectious diseases or tropical medicine consultation. ACT Rx is an induction and potentiation framework — not a substitute for parenteral therapy in severe disease.

7 REGULATORY FRAMEWORK & EVIDENCE BASE

7.1 Regulatory Status Summary

Component	Regulatory Classification	Notes
Artesunate 50 mg	WHO Essential Medicine; Schedule H (India); Rx-only	Approved for uncomplicated and severe malaria per WHO Treatment Guidelines 2022. Not approved for dengue — research use requires IRB clearance and informed consent.
Artemether SL Spray (60 mg)	Schedule H applies to artemether oral forms (India)	Sublingual formulation regulatory classification subject to national drug authority determination (CDSCO or equivalent). Confirm product registration status with Egg Pharma Medical Affairs before dispensing.
Berberine 400 mg	AYUSH-registered (Ayurvedic Pharmacopoeia of India)	OTC or Rx scheduling varies by jurisdiction. QTc and CYP3A4 interaction obligations apply regardless of scheduling status.
ACT Rx Combination Protocol	Not registered as a fixed-dose combination	Combination use under prescriber clinical judgement. All dengue applications are strictly exploratory research — IRB clearance and informed consent are mandatory.

7.2 Evidence Classification Framework

This handbook uses a tiered system to clearly distinguish the evidentiary basis of all pharmacological claims:

- No callout marker — Established published evidence (clinical trials, pharmacokinetic studies, peer-reviewed mechanistic research).
- NOTE callout — Established evidence with contextual qualification or application caveat.
- INFERRED FROM ESTABLISHED DATA callout — Mechanism is pharmacologically reasoned from published data in related contexts; direct clinical evidence in this specific application is not yet available.
- CLINICAL DIRECTIVE — Protocol instruction based on established pharmacology and/or standard clinical practice.
- WARNING — Safety information based on established risk data.

7.3 Key Evidence Base

Prescribers are encouraged to review primary sources before clinical application.

- World Health Organization. Guidelines for the Treatment of Malaria, 3rd Edition (2015), updated 2022. WHO Press, Geneva.
- Meshnick SR. Artemisinin: mechanisms of action, resistance and toxicity. International Journal for Parasitology. 2002;32(13):1655–1660.

- Tilley L, et al. Artemisinin action and resistance in Plasmodium falciparum. Trends in Parasitology. 2016;32(9):682–696.
- Imenshahidi M, Hosseinzadeh H. Berberis Vulgaris and Berberine: An Update Review. Phytotherapy Research. 2019;33(3):504–523.
- Yin J, et al. Berberine improves glucose metabolism through induction of glycolysis. American Journal of Physiology — Endocrinology and Metabolism. 2008;294(1):E148–E156.
- Shen N, et al. Berberine inhibits LPS-induced NF-κB-dependent inflammatory signalling. Archives of Pharmacal Research. 2015;38(10):1874–1882.
- Thapar MM, et al. Pharmacokinetics of artemether and lumefantrine in African and Asian patients. European Journal of Clinical Pharmacology. 2005;61(1):1–8.
- Adjei GO, et al. Artemisinin combination therapy for malaria — a review of pharmacokinetic drug interactions. Tropical Medicine & International Health. 2009;14(3):305–315.
- Pham TH, et al. Berberine inhibits P-glycoprotein in multidrug-resistant cancer cells. Anticancer Research. 2005;25:1953–1958. [P-gp inhibition basis; direct malaria PK interaction data not yet available.]
- Shan L, et al. Berberine analogue inhibits P-glycoprotein and reverses drug resistance. Cancer Biology & Therapy. 2009;8(2):182–189.
- Gazzinelli RT, et al. Innate sensing of malaria parasites. Nature Reviews Immunology. 2014;14(11):744–757.
- Ashley EA, et al. Spread of artemisinin resistance in Plasmodium falciparum malaria. New England Journal of Medicine. 2014;371(5):411–423.

7.4 Disclaimer

NOTE · This handbook is an educational and clinical reference document produced by Egg Pharma Research & Medical Affairs. It does not constitute regulatory approval documentation and does not substitute for peer-reviewed clinical guidelines or the independent clinical judgement of the treating practitioner. Where claims are inferred from established pharmacological data, they are identified as such throughout. All off-label applications, including dengue fever, require appropriate institutional review and informed patient consent. Egg Pharma accepts no liability for outcomes arising from deviation from the safety and monitoring protocols outlined herein. Version 2.0 — revised to remove unverified quantitative claims and clearly distinguish inferred from established evidence.