CLINTON HEALTH ACCESS INITIATIVE

Product Selection Guide: Caffeine Citrate for the Management of Apnea of Prematurity

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A guide to support national governments and procurement agencies in assessing and selecting quality-assured caffeine citrate products available in the sub-Saharan African market.

For the purposes of this guide, quality-assured products are defined as products that have been World Health Organization Prequalified (WHO PQ) and/or approved by a Stringent Regulatory Authority (SRA) or a WHO-Listed Authority (WLA).

Intended audience:

- Ministry of Health newborn and child health program managers and policymakers
- Procurement officers and supply chain managers
- Technical working groups and essential medicines committees
- Neonatal clinicians and professional associations
- Clinical guideline and protocol development committees
- Hospital-level pharmacy and neonatal unit managers

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1. Background and rationale

1.1 Purpose and scope

Prematurity is the leading cause of newborn deaths globally, responsible for approximately 816,673 neonatal deaths in 2024 and contributing to 36% of all neonatal mortality.[1] The burden is especially severe in sub-Saharan Africa (SSA), where prematurity accounts for an estimated 40% of neonatal deaths.[2]

A significant proportion of these deaths are associated with preventable and treatable complications of prematurity during the neonatal period. Among these, apnea of prematurity (AOP) is one of the main drivers of morbidity and mortality among preterm infants. The incidence of AOP is strongly inversely related to gestational age: it affects nearly all infants born at less than 28 weeks, about 85% of infants born at 30 weeks, and approximately 20% of those born at 34 weeks, with incidence continuing to decline in late preterm infants.[3] AOP can lead to hypoxia, bradycardia, feeding disruption, extended hospitalization, and longer-term neurodevelopmental consequences if not effectively managed.[4] AOP can often be both prevented and treated effectively with high-quality neonatal care, including thermal regulation, respiratory support, careful monitoring, Kangaroo Mother Care, and timely use of optimal pharmacologic therapy such as caffeine citrate.

Caffeine is recommended for the treatment of apnea in preterm infants born before 37 weeks' gestation and may also be considered for the prevention of apnea in preterm infants born before 34 weeks' gestation.[5] However, access to caffeine citrate remains limited in many low- and middle-income countries (LMICs), where aminophylline continues to be widely used despite its narrower therapeutic index and adverse effects in neonates.[6] Expanding access to caffeine citrate could meaningfully reduce preventable deaths among preterm infants in high-burden settings.

Since 2022, caffeine citrate procurement volumes in SSA are estimated to have grown more than tenfold, and in 2023, the Clinton Health Access Initiative (CHAI) negotiated a price reduction of over 70% in Kenya[7] that has since been expanded to other African markets. At least six quality-assured (QA) products from four different manufacturers are available across SSA, with the registration footprint expanding each year. Rapid market growth has improved availability and reduced prices, but it has also complicated procurement decisions. Governments must now choose between multiple concentrations, presentations, administration routes, and manufacturers, each with different implications for safety, wastage, price, and supply security. This fragmentation creates significant risks, including:

- **Fragmented, low-volume procurement:** a fragmented supplier base can undercut the negotiating leverage that has driven price reductions to date, as pooled/negotiated procurement becomes harder to coordinate across multiple products, which can undermine long-term market stability and supply security;
- **Mismatch between the different product specifications/options (e.g., concentration, presentation, route of administration) and intended use:** may result in wastage, operational inefficiencies, or dosing and administration errors, including confusion between caffeine citrate and caffeine base concentrations or differences in product labeling; and
- **Outdated training materials and job aids:** facility-level tools (standing orders, dosing charts, discharge checklists) risk becoming outdated or inconsistent if they don't keep pace with available in-country product options.

CHAI developed this guide to help national governments, procurement agencies, and program managers select and procure appropriate QA caffeine citrate products for the prevention and treatment of AOP. Specifically, it aims to:

- Support government-led procurement and formulary decisions through clear, evidence-based specification criteria; and
- Provide policymakers and procurement stakeholders with a framework of key criteria and considerations to support informed decisions on caffeine citrate product selection.

1.2 What is caffeine citrate?

Caffeine citrate is widely regarded as the preferred pharmacological treatment for apnea of prematurity, given its favorable safety profile, wider therapeutic index, and longer half-life compared with other methylxanthines such as aminophylline and theophylline. WHO strongly recommends caffeine for the treatment of apnea and to facilitate extubation in preterm infants born before 34 weeks and conditionally recommends it for prevention of apnea in infants born before 34 weeks' gestation.[8]

Caffeine citrate has been shown to **reduce apnea episodes by approximately 80%** compared to placebo (Henderson-Smart & Davis, 2010), and the landmark CAP trial demonstrated broader benefits:

- ~36% reduction in bronchopulmonary dysplasia (Schmidt et al., 2006)
- 18% lower risk of neurodevelopmental disability at 18 months (Schmidt et al., 2007)
- Reduced duration of mechanical ventilation, and improved outcomes at age 11 years (Schmidt et al., 2017).

Caffeine citrate can be administered orally or intravenously, depending on the product formulation and approved route of administration. Oral administration is well absorbed, with near-complete bioavailability reported in preterm infants; some injectable formulations are also approved for oral administration.[9] Treatment is typically initiated with a loading dose of 20 mg/kg caffeine citrate, followed by a maintenance dose of 5 mg/kg once daily beginning approximately 24 hours after the loading dose.[10] The maintenance dose may be increased to 10 mg/kg once daily if apnea persists.[11] Caffeine has a long half-life in preterm infants (typically 72–96 hours; range 40–230 hours, decreasing with advancing corrected gestational age),[12] allowing once-daily dosing and prolonged therapeutic activity. In clinical practice, treatment commonly extends over several weeks, particularly for extremely preterm infants.

In addition to its clinical effectiveness, caffeine citrate possesses practical characteristics that support routine neonatal use. For example, it does not require cold-chain storage, making it well suited for neonatal care in LMICs.

2. Available quality-assured products

Differences in specifications for QA caffeine citrate products can have important implications for clinical use, procurement, and program implementation. Variations in concentration (e.g., 10, 20, or 25 mg/mL), presentation and pack size (e.g., 1, 2, or 3 mL ampoules or 5 mL vials), and intended route of administration (IV, oral, or both) can affect dosing accuracy, medicine wastage, training requirements, and procurement complexity.

For most neonatal programs, key clinical considerations include whether a concentration can be accurately dosed in very low birth weight infants, whether pack sizes align with typical facility patient volumes, and whether introducing additional concentrations could increase the risk of medication errors. Different products on the market have different specifications that governments must consider when making decisions on clinical guidance and procurement.

Table 1 provides an overview of QA caffeine citrate products currently available in SSA markets that meet the quality assurance criteria applied in this guidance (WHO prequalified or SRA/WLA approved). This list is not exhaustive and excludes caffeine citrate products that are registered and quality-assured by national medicines regulatory authorities but do not meet the quality assurance criteria used in this guidance (for example, Tasa Pharma has a 10 mg/1 mL caffeine citrate product registered in Kenya, while SO-CVS Investment Limited, a Ghana FDA-approved local pharmaceutical manufacturer, has a 20 mg/mL caffeine citrate product registered in Ghana). Countries should refer to their national medicines regulatory authority for information on nationally registered caffeine citrate products.

Key product terms

- **Formulation** is the pharmaceutical form of the product, e.g., an oral solution or solution for injection/infusion.
- **Route of administration** is how the product is given, e.g., oral/enteral or intravenous (IV).
- **Concentration** is the amount of caffeine citrate in each milliliter, expressed as mg/mL.
- **Presentation** is the volume supplied and container type, e.g., a 1 mL ampoule or 5 mL vial.
- **Total drug content** is the total amount of caffeine citrate in one container, expressed in milligrams (mg).
- **Caffeine base** is the active caffeine part. Unless explicitly stated otherwise, all doses, concentrations, and total drug contents in this guide refer to caffeine citrate. 20 mg caffeine citrate is equivalent to 10 mg caffeine base.

Table 1: Quality-assured products overview

Manufacturer (HQ country) Product name	Concentration and route(s) of administration	Presentation (Pack size)	Supply chain requirement	Regulatory status
Ethypharm – Macarthys Laboratories Limited (UK) **Caffeine citrate solution for injection**	10 mg/mL IV or oral	1 mL ampoule (10 mg/amp)	Preservative-free; do not store above 30°C.	SRA/WLA + WHO PQ[13]
Ethypharm – Macarthys Laboratories Limited (UK) **Caffeine citrate oral solution**	10 mg/mL oral	5 mL vial (50 mg/vial)	Preservative-free; do not store above 25°C.	SRA/WLA + WHO PQ[14]

Manufacturer (HQ country) Product name	Concentration and route(s) of administration	Presentation (Pack size)	Supply chain requirement	Regulatory status
Chiesi Foundation (Italy) **Peyona caffeine citrate solution**	20 mg/mL IV or oral	3 mL ampoule (60 mg/ampoule)	Preservative-free; no cold chain needed. Do not store above 30°C.	SRA/WLA + WHO PQ[15]
Chiesi Foundation (Italy) **Peyona caffeine citrate solution**	20 mg/mL IV or oral	1 mL ampoule (20 mg/amp)	Preservative-free; no cold chain needed. Chemical and physical compatibility of the diluted solution has been demonstrated for 24 hours at 25°C and at 2–8°C.	SRA/WLA[16]
Gennisium Pharma (France) **Gencebok® caffeine citrate solution**	10 mg/mL IV or oral	1 mL ampoule (10 mg/amp)	Preservative-free; no special storage requirement; no cold chain needed.[17]	SRA/WLA[18]
Cooper (France) **Citrate de caféine Cooper / Caffeine citrate solution**	25 mg/mL IV or oral	2 mL ampoule (50 mg/ampoule)	Preservative-free; store protected from light; no temperature restriction.	SRA/WLA[19]

Source: *CHAI market engagement data and public regulatory information.*

Note: *Verify pricing and shelf life with suppliers at time of procurement. All IV products are preservative-free and single-use; the 5 mL oral vial is single-use, preservative-free, and any unused solution should be discarded. Certain preservatives (e.g., benzyl alcohol) are contraindicated in preterm infants.[20]*

Three observations are particularly important given the available product landscape:

- First, lower-concentration products (10 mg/mL) generally provide greater dosing flexibility for very small infants and may reduce the risk of volume-calculation errors.
- Second, larger presentations may offer operational advantages in higher-volume facilities but can result in substantial wastage when used for small infants or in low-volume settings.
- Finally, with multiple manufacturers now active in the market, procurement decisions should assess quality assurance, clinical and operational considerations, and supply reliability in addition to price.

3. Product selection

3.1 Selection criteria

Once a product has met minimum quality and regulatory requirements (see Annex A), procurement teams should evaluate additional considerations that will influence implementation success, supply reliability, and overall value for money, including:

1. **Is the product quality-assured and registered?** Determine whether the product has approval from a **WHO-Listed Authority (WLA), Stringent Regulatory Authority (SRA), or WHO Prequalification (PQ)**, as applicable, and confirm its national registration status. Nationally registered products that do not meet these quality-assurance criteria should be assessed for procurement eligibility in accordance with applicable national regulatory requirements and procurement policies. Where import waivers are used, identify a clear transition plan toward full national registration.
2. **Is the product safe and easy to use at the intended level of care?** Assess whether the product is appropriate for its intended use, including **facility-based IV or oral administration**. Assess whether the concentration enables **accurate dosing in preterm infants, including very low birth weight (VLBW) infants**, using equipment available at the point of care, while minimizing the risk of dosing and medication errors.
3. **Do the pack size and presentation fit typical patient volumes?** Consider whether the pack size and presentation are appropriate for expected patient volumes and treatment patterns, including the potential for **product wastage among preterm and VLBW infants**. However, do not consider wastage in isolation: a product with a larger dosage content may still offer better value if its acquisition price is sufficiently lower than that of a product with a smaller dosage content.
4. **Can the supplier reliably meet demand?** Assess the supplier's **manufacturing capacity, supply history, regulatory compliance, and delivery performance,** as well as its ability to meet projected demand consistently and mitigate potential supply disruptions. Note that national-level stock availability does not by itself ensure availability at the point of care; last-mile distribution should be considered in national supply chain planning.
5. **Does the product align with national treatment protocols and existing training materials?** Assess whether the product's concentration, presentation, and route of administration are consistent with current national AOP treatment protocols, standard treatment guidelines, dosing charts, and job aids, and with the training healthcare workers have already received. Where a change in product specification is being considered, account for the cost, time, and medication-safety implications of revising protocols and dosing charts, updating job aids, and reorienting staff, and weigh these against the expected benefits of the new product.
6. **Does the product provide value for money after accounting for wastage?** Compare products based on the **cost of delivering a completed treatment course**, considering acquisition price, expected wastage, pack size, and other relevant costs rather than comparing price per vial or per mL alone. Where applicable, governments may wish to consider compatibility with national medicine financing and reimbursement mechanisms.

Note: When comparing the affordability of different caffeine citrate products, consider several factors beyond the price of an individual vial or ampoule.

- **Compare price per mg of caffeine citrate**, rather than price per vial or mL, to enable meaningful comparison across product options (e.g., concentration and presentation).

- **Consider the total treatment-course cost**, including product price, total drug content, potential wastage, freight, and other associated procurement costs. A lower unit price may not translate into a lower overall treatment cost if the product presentation or total drug content results in greater wastage. Larger presentations (e.g., 50 or 60 mg caffeine citrate) may offer better value than a smaller container if the acquisition price is sufficiently lower and if they can be used safely within the approved single-use or validated preparation requirements.
- **Check donor/multilateral procurement eligibility** since it affects which procurement channels and concessional pricing are available for a given product.
- **Consider other downstream costs**, such as training and inventory management, where differences between product specifications may affect the resources required for implementation.

3.2 Product fit for use case

Product selection should consider the intended use and setting. **Table 2** summarizes key considerations, including dose-volume fit, authorized routes of administration, wastage, and medication safety. See Annex B for an illustrative example of dose volumes and potential wastage.

Table 2: Product selection considerations: dose-volume fit, wastage, and safety

Concentration and presentation	Authorized routes of administration	Loading dose fit (per WHO 20 mg/kg/dose)	Maintenance dose fit (per WHO 5–10 mg/kg/day)	Wastage and medication-safety considerations
Strength: 10 mg/mL **Container: 1 mL ampoule** **Total drug content: 10 mg caffeine citrate per ampoule**	IV infusion or oral	1 mL ampoule contains 10 mg. This may cover the full loading dose for an infant weighing up to 0.5 kg; larger infants require more than one ampoule.	Produces larger, generally more measurable volumes than higher concentrations for very small infants. For example, for a 1 kg infant the maintenance dose is 0.5–1 mL at 10 mg/mL, compared with 0.2–0.5 mL at 20–25 mg/mL.	Small single-use ampoules may reduce waste for lower maintenance doses but may require multiple ampoules for loading doses in larger infants. If multiple concentrations are stocked, use concentration-specific labels, storage segregation, dosing charts, and double-check procedures/job aids.
Strength: 10 mg/mL **Container: 5 mL vial** **Total drug content: 50 mg caffeine citrate per vial**	Oral	One 5 mL vial contains 50 mg, enough for the full 20 mg/kg loading dose of an infant weighing up to 2.5 kg.	Produces larger, generally more measurable volumes than higher concentrations for very small infants. For example, for a 1 kg infant the maintenance dose is 0.5–1 mL at 10 mg/mL, compared with 0.2–0.5 mL at 20–25 mg/mL.	Total content (50 mg) is well above a single maintenance dose (5–10 mg/kg/day) for most preterm infants; the residual volume may require disposal after a single administration, in accordance with the approved product information.

Concentration and presentation	Authorized routes of administration	Loading dose fit (per WHO 20 mg/kg/dose)	Maintenance dose fit (per WHO 5–10 mg/kg/day)	Wastage and medication-safety considerations
Strength: 20 mg/mL **Container: 1 mL ampoule** **Total drug content: 20 mg caffeine citrate per ampoule**	IV infusion or oral	Well-matched to a loading dose for very small infants; single-ampoule simplicity.	Higher concentration means very small maintenance draw volumes; precision at the smallest weights depends on available syringe graduation.	Low wastage for loading; administration-precision risk for maintenance doses for very low birth weight infants. Avoid co-locating with 10 mg/mL products without strong concentration-specific labeling and job aids.
Strength: 20 mg/mL **Container: 3 mL ampoule** **Total drug content: 60 mg caffeine citrate per ampoule**	IV infusion or oral	Comfortably covers loading doses for larger infants in one ampoule.	Higher concentration means very small maintenance draw volumes; precision at the smallest weights depends on available syringe graduation.	Higher potential for residual-volume wastage when used as a single-use presentation, particularly for maintenance doses in smaller infants, where the required dose may represent a small proportion of the container volume. Compare wastage-adjusted cost rather than unit cost or container size alone.
Strength: 25 mg/mL **Container: 2 mL ampoule** **Total drug content: 50 mg caffeine citrate per ampoule**	IV infusion or oral	Ampoule content exceeds a typical loading dose for the smallest infants; residual volume may require disposal after a single administration, in accordance with approved product information.	Highest concentration in this set; maintenance draw volumes are smallest, raising measurement-precision concerns at very low birth weights.	Produces the smallest dose volumes, requiring attention to syringe accuracy, dose verification, labeling, and staff competency. Incomplete emptying of the syringe may result in residual drug wastage and under-dosing, particularly for smaller doses. Product selection should consider route authorization, available equipment and safeguards, supply reliability, and wastage-adjusted cost.

Additional notes:

a. All strengths, total content, and doses are expressed as caffeine citrate, not caffeine base. Product choice should consider the smallest dose volume that must be measured, expected infant weights, patient throughput, route, local wastage-adjusted treatment course cost, supply reliability, and ability of providers to safely manage one or more concentrations in their facility systems.
b. Opened preservative-free single-use containers are meant to be discarded according to the approved product information and not retained for later use.
c. Authorized route(s), administration requirements, storage conditions, and in-use requirements must be verified in the current approved product information for the exact product, presentation, and receiving market. Products should not be administered by a route not authorized in their approved label or national guidance.

Programmatic and facility trade-offs of concentration selection: No single concentration is optimal in every setting. The 10 mg/mL concentration produces larger, more easily measurable volumes for very small infants and may reduce the risk of inaccurate measurement during maintenance dosing. The 20 mg/mL and 25 mg/mL concentrations require lower administration volumes, including for loading doses, which may offer operational advantages where appropriate dosing equipment and concentration-specific safeguards are reliably in place. Because dose volumes are smallest at these concentrations, particular attention is needed to syringe accuracy, labelling, and staff competency, especially at 25 mg/mL. For preservative-free, single-use presentations, potential wastage of unused product should be considered when comparing products. Where national programs have approved policies or standard operating procedures (SOPs) for centralized preparation, these should be followed. This guide does not recommend or establish centralized preparation practices.

3.3 Single product option vs. multiple product options

The decision to standardize procurement to a single product specification or to procure multiple product specifications is primarily an operational consideration. Multiple product specifications may allow countries to accommodate different clinical or care-setting requirements, but may also affect procurement and supply, quality assurance, cost, training, and safe use. Table 3 highlights the key trade-offs associated with procuring a single versus multiple product specifications.

Table 3: Formulation selection: clinical, operational, and safety considerations

Criteria	Single product	Multiple product options
Patient safety	Can reduce the risk of errors associated with substituting between different concentrations and may simplify prescribing, dispensing, administration, and training.	Safe use requires matching the prescribed dose to the product concentration. Where multiple concentrations are used, concentration-specific protocols, differentiated labeling, and staff training are needed to minimize the risk of concentration-related dosing errors.
Clinical fit	May not suit every clinical and operational use case: • A single concentration or presentation may result in residual waste when the total drug content per container is substantially greater than the individual loading or maintenance dose. • An oral-only product may not be appropriate when IV administration is clinically required, or enteral administration is not feasible. • A single chosen concentration may also require difficult-to-measure dose volumes for some infant weights. • These trade-offs should be assessed against the safety and operational advantages of national standardization.	Allows facilities to select a concentration and presentation that better match expected infant weights, loading and maintenance dose volumes, authorized route(s) of administration, patient numbers, and local wastage-adjusted price. For example, a larger single-use container may be cost-efficient for loading doses or in higher-volume settings, while a smaller container may reduce residual waste for low-weight infants and maintenance doses. Multiple options can also ensure that an oral/enteral product is available when enteral administration is clinically appropriate. These benefits should be weighed against the added complexity and medication safety risks of managing more than one concentration and presentation.

Criteria	Single product	Multiple product options
Facility-level considerations	Not applicable when one product is used across all indications.	Requires clear guidance on substitution between product specifications, concentration-specific dose-volume charts, differentiated labeling and storage, staff training, and supervision. Any substitution between concentrations should follow an approved protocol specifying the authorized route, dose-volume conversion, and appropriate prescriber/pharmacist verification.
Supply chain and QA burden	Low complexity: one lot-release/QA/pharmacovigilance process, simpler freight.	Higher complexity: independent stock management, lot release, and reporting per line item.
Supplier competition & minimum order quantities	No competing bid if only one manufacturer is registered for the chosen product specification, weakening negotiating power. However, standardizing on a single product may increase volumes and support volume-based price reductions.	Broader competition and supply resilience; however, splitting procurement volumes may reduce volume-based purchasing leverage and increase procurement and inventory-management complexity. The choice should therefore balance supply-security risks with the benefits of volume consolidation and the capacity to manage multiple product options safely.
Price comparison	Straightforward unit-cost comparison.	Compare prices on a cost-per-mg basis and also consider potential wastage when assessing overall cost.
Training and job aids	Prescribers, nurses, and pharmacists work with one product, one concentration, one volume calculation.	Staff must be trained on which product specification to use for which indication and how to convert volumes per the different permutations of concentration and presentation; bedside job aids must cover every specification in use.

4. Conclusion

This document summarizes the available QA caffeine citrate products and the key considerations and nuances to assess when deciding which and how many different caffeine citrate products to procure. Key factors include product quality and regulatory status, patient safety and clinical fit, total treatment course cost, procurement and supply considerations, and the operational requirements of managing more than one product specification. Product selection will ultimately be shaped by how governments and relevant stakeholders in each country weigh these different factors.

Annex A: Minimum procurement specification checklist

Item	Required standard
Active pharmaceutical ingredient (API)	"Caffeine citrate" stated explicitly as the API, not "caffeine," "caffeine base," or "caffeine benzoate".
Concentration	Clearly specified, with the total caffeine citrate content per container also stated. Do not accept unlabeled or ambiguous concentrations.
Preservatives	The presence and type of preservatives should be clearly stated in the approved product information (e.g., preservative-free, with no sodium benzoate or benzyl alcohol).
Presentation	Specify container type (e.g., vial or ampoule), volume, and total caffeine citrate content per container; consider suitability for intended use and potential wastage.
Available route(s) of administration	Authorized route(s) of administration should be clearly stated and appropriate for the intended use (e.g., oral or intravenous).
Sterility	Injection/infusion: Verify that the product is sterile and meets applicable pharmaceutical and regulatory requirements for sterile products. Oral: Sterility is not required; verify compliance with the approved product specification.
Packaging	Consider the container type (e.g., single-use or multi-dose), including requirements for disposal of unused product and, for multi-dose containers, safe handling, storage, and use in accordance with the approved product information and applicable national requirements.
Shelf life	Minimum remaining shelf life at delivery should be specified in procurement requirements, with the delivery point defined in the procurement agreement (e.g., the central medical store or warehouse, regional or district store, or health facility). Requirements should reflect supply lead times and anticipated consumption, with procurement quantities aligned to facility-level demand to reduce the risk of expiry, particularly at facilities with low utilization. Stock levels should be monitored, and products redistributed between facilities where needed, to minimize wastage from expiry.
Storage	Confirm the specific storage range against the manufacturer's product specification sheet and label.
Quality assurance	WHO PQ and/or SRA/WLA approved, current Good Manufacturing Practice (GMP) certification, and availability of a batch-specific Certificate of Analysis (CoA) where required by national procurement or quality control procedures.
Labeling	API "Caffeine citrate" and concentration (mg/mL and mg/vial); preservative status; route of administration; contraindications; and language requirements, in accordance with applicable national regulatory requirements.
Package insert	Package insert or product information leaflet (available in the required language) specifying dosing, administration instructions, contraindications, clinically relevant drug interactions (including effects of CYP enzyme inhibitors and inducers such as cimetidine, ketoconazole, phenytoin, and phenobarbitone), and adverse effects.
Pharmacopoeial standard	Complies with a recognized pharmacopoeial standard, where an applicable monograph exists (e.g., United States Pharmacopeia [USP], British Pharmacopoeia [BP], or European Pharmacopoeia [Ph. Eur.]), or with the approved product specification where no applicable pharmacopoeial monograph exists.
Country registration	Valid national marketing authorization or confirmed import waiver prior to delivery.

Annex B: Illustrative example on dose volumes and potential wastage

The example below illustrates how infant weight, prescribed dose, product concentration, total content per container, and the availability of suitable measurement and administration devices jointly affect dose accuracy and potential residual-volume wastage. Products should be prepared, administered, and any unused contents discarded in accordance with the manufacturer's approved product information and applicable national requirements. For preservative-free single-use presentations, potential residual-volume wastage should be considered when comparing products. Where national programs have approved policies or SOPs for centralized preparation, these should be followed; this guide does not recommend or establish such practices.

Illustrative dose scenario	10 mg/mL, 1 mL ampoule 10 mg total	10 mg/mL, 5 mL vial 50 mg total	20 mg/mL, 1 mL ampoule 20 mg total	20 mg/mL, 3 mL ampoule 60 mg total	25 mg/mL, 2 mL ampoule 50 mg total
0.5 kg infant Loading dose: 20 mg/kg = 10 mg	Withdraw 1.0 mL. 1 ampoule used; no nominal residual.	Withdraw 1.0 mL. 40 mg remains; discard if single-use.	Withdraw 0.5 mL. 10 mg remains; discard if single-use.	Withdraw 0.5 mL. 50 mg remains; discard if single-use.	Withdraw 0.4 mL. 40 mg remains; discard if single-use.
1 kg infant Loading dose: 20 mg/kg = 20 mg	Withdraw 2.0 mL. 2 ampoules required.	Withdraw 2.0 mL. 30 mg remains; discard if single-use.	Withdraw 1.0 mL. 1 ampoule used; no nominal residual.	Withdraw 1.0 mL. 40 mg remains; discard if single-use.	Withdraw 0.8 mL. 30 mg remains; discard if single-use.
1 kg infant Maintenance dose: 5 mg/kg/day = 5 mg	Withdraw 0.5 mL. 5 mg remains; discard if single-use.	Withdraw 0.5 mL. 45 mg remains; discard if single-use.	Withdraw 0.25 mL. 15 mg remains; discard if single-use.	Withdraw 0.25 mL. 55 mg remains; discard if single-use.	Withdraw 0.2 mL. 45 mg remains; discard if single-use.
Measurement and delivery implications	Larger withdrawal volumes may be easier to measure; multiple ampoules may be needed for loading doses.	Larger withdrawal volumes, but potentially substantial residual waste for lower doses.	Smaller maintenance volumes require appropriately graduated devices and dose verification.	Very small maintenance volumes and high potential residual-volume waste for individual doses.	Smallest withdrawal volumes in this comparison; requires particular attention to syringe graduation, delivery-device dead space, dose verification, and staff competency.

Notes

- All doses, concentrations, and total contents are expressed as caffeine citrate, not caffeine base. The scenarios use the loading dose of 20 mg/kg and maintenance dose of 5 mg/kg/day.
- Residual amounts are container residuals calculated as total container content minus the prescribed dose. They do not represent a measured wastage rate and do not account for any drug retained in the syringe, hub, needleless connector, enteral tubing, or other administration device; drug retention in these devices is a documented problem that can lead to medication errors, particularly under-dosing.
- Preservative-free single-use products must be prepared, administered, and any unused content discarded in accordance with the current manufacturer-approved product information and applicable national requirements.

- The smallest withdrawn volumes, such as 0.1–0.25 mL, require devices with suitable graduations and staff competency in preparation and administration. A multi-center observational study of neonatal intensive care unit (NICU) IV medicine preparations found frequent accuracy errors and identified product characteristics, syringe selection, and preparation technique as important determinants.[21]
- This table is illustrative and is **not** a dosing chart. Facilities should use approved product-specific dose-volume charts and procedures.

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[15] AP003- Chiesi Peyona Caffeine citrate 60 mg/3 mL, solution for infusion- WHO PQ 10 July 2026

[16] Chiesi Peyona Caffeine citrate 20 mg/mL, Summary of product characteristics

[17] Gencebok® summary of product characteristics, European Medicines Agency 2020

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