

WHO-PQ recommended clinical and preclinical information for the health care provider

This information reflects the recommendations of current WHO guidelines and the scope of WHO's prequalification programme.

1. TYPE OF THE MEDICINAL PRODUCT

[AP003 trade name]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caffeine citrate 60 mg/3 mL

For product-specific information, see WHOPAR part 4.

3. PHARMACEUTICAL FORM

Solution for infusion

For product-specific information, see WHOPAR part 4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[AP003 trade name] is indicated for:

- treating apnoea in preterm neonates
- preventing apnoea after extubation of preterm neonates of gestational age up to 37 weeks
- preventing apnoea in preterm neonates of gestational age less than 34 weeks.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

Treatment of apnoea in preterm neonates

Initial dose: caffeine citrate 20 mg/kg by mouth as a single dose
then after 24 hours, caffeine citrate 5 mg/kg daily for 6 weeks or until there is adequate clinical response.

Extubation of preterm neonates born up to 37 weeks after gestation

Initial dose: caffeine citrate 20 mg/kg by mouth as a single dose
then after 24 hours, caffeine citrate 5 mg/kg daily for 6 days.

Prevention of apnoea in preterm neonates born before 34 weeks' gestation

Initial dose: caffeine citrate 20 mg/kg by mouth as a single dose
then after 24 hours, caffeine citrate 5 mg/kg daily for 6 weeks or according to clinical needs.

Note

Doses are expressed as **caffeine citrate**; 2 mg of caffeine citrate is equivalent to 1 mg caffeine (base).

Plasma caffeine concentration

Plasma caffeine concentration monitoring is rarely necessary. It may be used to adjust the daily dose when higher dose is needed or if toxicity is suspected. Caffeine concentrations associated with clinical benefit range between 8 and 30 mg/litre; toxicity is unlikely with plasma concentration below 50 mg/litre.

Consumption of large amounts of caffeine by the mother before delivery may mean that the neonate already has circulating caffeine before [AP003 trade name] is given. Previous treatment of the neonate with theophylline can also contribute to plasma caffeine concentration.

Renal impairment

Daily doses of caffeine citrate may need to be reduced in renal impairment to prevent accumulation. The dose can be adjusted according to clinical response and, if available, measurement of caffeine concentration in blood.

Hepatic impairment

Hepatic function does not affect the clearance of caffeine in very premature neonates but in an older infant, hepatic disease may impair caffeine metabolism and the dose of caffeine may need to be reduced.

Method of administration

[AP003 trade name] should be given orally (e.g. through a nasogastric tube) regularly every 24 hours.

4.3 Contraindications

Hypersensitivity to caffeine citrate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Inadequate response

If apnoea in the premature infant does not respond to adequate doses of caffeine citrate, other causes of apnoea should be considered.

Seizure disorders

Caffeine citrate must be used with extreme caution in neonates with seizure disorders since seizures have occurred with caffeine overdose.

Cardiovascular disorders

Caffeine citrate should be used cautiously in neonates with cardiovascular disease or in those whose cardiotocograph before birth showed unusual rhythm disturbances. Caffeine citrate may cause sinus tachycardia.

Renal and hepatic impairment

The frequency of adverse effects may be increased in very premature neonates with renal or hepatic impairment. Care is required with the dose in these neonates to avoid toxicity.

Gastro-intestinal disorders

Pre-term neonates receiving caffeine citrate should be monitored for the development of necrotising enterocolitis although a causal relationship between caffeine citrate and necrotising enterocolitis has not been established. Reduced gastric acid secretion may promote bacterial overgrowth and increase the risk of necrotising enterocolitis.

Caffeine citrate should be used with caution in neonates suffering from gastro-oesophageal reflux since caffeine citrate may exacerbate the condition.

Metabolic changes and diuresis

Caffeine citrate increases metabolic rate, which may result in higher energy and nutritional requirements.

The diuretic effect of caffeine citrate may necessitate correction of fluid and electrolyte disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Caffeine metabolism is limited in preterm neonates because of their immature hepatic enzyme systems. As these systems mature, caffeine is mainly metabolised by CYP1A2, and substrates, inhibitors and inducers of CYP1A2 can affect caffeine metabolism in older infants.

Caffeine is a methylxanthine and concurrent use of other methylxanthines such as aminophylline and theophylline should be avoided. Aminophylline or theophylline are metabolised to caffeine. When switching treatment to [AP003 trade name] it is important to consider that caffeine may be present in the blood from previous treatment.

Medicines that suppress gastric acid secretion (such as H₂-receptor blockers and proton-pump inhibitors) may allow bacterial overgrowth. Therefore, co-administration of these medicines with caffeine citrate may increase the risk of necrotising enterocolitis.

Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If used concurrently, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Caffeine readily crosses the placenta into the fetal circulation. Consumption of large amounts of caffeine before delivery may mean that the neonate already has circulating caffeine before [AP003 trade name] is given.

Breast-feeding

Breast-feeding mothers of neonates treated with [AP003 trade name] should not ingest caffeine-containing drinks, foods or medicines, since caffeine passes into breast milk.

Fertility

Treatment of the neonate with caffeine citrate is not likely to have any effect on fertility. The effect of caffeine in animal reproduction studies is not relevant to caffeine citrate treatment of preterm neonates.

4.7 Effects on ability to drive and use machines

The effect of [AP003 trade name] on the performance of skilled tasks is not relevant to neonates.

4.8 Undesirable effects

Summary of the safety profile

The adverse effects of caffeine citrate, predicted from its pharmacology and toxicology, include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects such as tachycardia, arrhythmia, hypertension and increased stroke volume, metabolic effects such as hyperglycaemia. These effects are dose related.

Tabulated list of adverse reactions

Adverse reactions of [AP003 trade name] are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations

Not known sepsis

Immune system disorders

Rare hypersensitivity reaction

Metabolism and nutrition disorders

Common	hyperglycaemia
Not known	hypoglycaemia, failure to thrive, feeding intolerance

Nervous system disorders

Uncommon	convulsion
Not known	irritability, jitteriness, restlessness, brain injury

Ear and labyrinth disorders

Not known	deafness
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Cardiac disorders

Common	tachycardia
Uncommon	arrhythmia
Not known	increased left ventricular output and increased stroke volume

Gastrointestinal disorders

Not known	regurgitation, increased gastric aspirate, necrotising enterocolitis
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General disorders and administration-site conditions

Common	infusion-site phlebitis, infusion-site inflammation
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Investigations

Not known	increased urine output, raised urine sodium and calcium, decreased haemoglobin, decreased thyroxine
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Description of selected adverse reactions

Use of methylxanthines (such as caffeine) may be associated with the development of necrotising enterocolitis, a condition that can lead to significant morbidity and mortality. However, a causal relationship has not been established between the use of caffeine citrate and necrotising enterocolitis. Preterm neonates should be monitored for the development of necrotising enterocolitis.

Brain injury, convulsion and deafness occurred in a clinical study involving preterm neonates but these effects were more frequent in neonates receiving placebo.

Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment.

Transient fall in thyroxine (T4) has been reported in neonates at the start of treatment but thyroxine decrease is not sustained with continuing treatment.

There is no evidence that treatment of preterm neonates causes long-term effect on neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine is unlikely to aggravate cerebral hypoxia or exacerbate any resulting damage.

Adverse reactions of caffeine citrate may be more frequent in premature neonates with renal or hepatic impairment. Such reactions mostly include cardiac disorder (tachycardia and one report of arrhythmia).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Plasma caffeine levels following overdose have ranged between 50 and 350 mg/litre.

Signs and symptoms of overdose

Signs and symptoms of caffeine overdosage reported in neonates and premature neonates include jitteriness, tachycardia, tachypnoea, opisthotonos, rigidity and tonic-clonic movements, hypokalaemia, fine tremor of the extremities, restlessness, gastric irritation, gastro-intestinal haemorrhage, increased white blood cell count, and non-purposeful jaw and lip movements.

Effects from gross overdose include fever, agitation, hyperexcitability, hypertonia, gastric residues, distended abdomen, metabolic acidosis, hyperglycaemia and elevated urea levels. No deaths from caffeine overdose have been reported in preterm neonates.

One case of caffeine overdose was complicated by intraventricular haemorrhage and long-term neurological sequelae. In another case, circulation was compromised and the neonate developed vomiting and seizures.

Management

Caffeine overdose in preterm neonates is managed by supportive measures. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected. Previous cases reported resolved satisfactorily.

Caffeine concentration in the blood may be monitored during management of an overdose.

Convulsions may be treated with intravenous administration of an anticonvulsant (such as phenobarbital, phenytoin or levetiracetam).

In severe overdose, exchange transfusion should be considered. In one case, each transfusion reduced plasma caffeine concentration by 40 mg/litre.

5. PHARMACOLOGICAL PROPERTIES

Information on pharmacological properties is shown in the product information as approved by the reference authority, stated in WHOPAR part 1. Additional data for those uses approved by WHO may be found in the references given at the end of this document.

6. PHARMACEUTICAL PARTICULARS

Information on the pharmaceutical particulars is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

If the “special precautions for storage” as assessed by PQT/MED differ from those approved by the reference authority, this is stated in WHOPAR part 1.

7. SUPPLIER

Information on the supplier is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

The WHO reference number is shown in WHOPAR part 1

9. DATE OF PREQUALIFICATION

The date of prequalification can be found in WHOPAR part 1.

10. DATE OF REVISION OF THE TEXT

July 2026

References

WHO recommendations for care of the preterm or low birth weight infant. Geneva: World Health Organization; 2022 (<https://iris.who.int/server/api/core/bitstreams/707c8feb-e4e4-4e5c-b029-b78202c67cc7/content>, accessed 22 November 2025).

Caffeine Citrate 10mg/ml Oral Solution (Macarthy's Laboratories Limited): summary of product characteristics. MHRA; 4 September 2018 (available at: <https://products.mhra.gov.uk>, accessed 22 November 2025)

Caffeine Citrate 10mg/ml Solution for Injection (Macarthy's Laboratories Limited): summary of product characteristics. MHRA; 31 March 2020 (available at: <https://products.mhra.gov.uk>, accessed 22 November 2025)

Peyona 20 mg/mL solution for infusion; summary of product characteristics. EMA; 18 September 2024 (https://www.ema.europa.eu/en/documents/product-information/peyona-epar-product-information_en.pdf, accessed 9 December 2025)

Section 4.9

Pressler RM, Abend NS, Auvin S, et al. Treatment of seizures in the neonate: Guidelines and consensus-based recommendations—Special report from the ILAE Task Force on Neonatal Seizures. *Epilepsia*. 2023;64:2550–2570. doi: 10.1111/epi.17745.

Section 5.1

Marques KA, Bruschetti M, Roehr CC, et al. Methylxanthine for the prevention and treatment of apnea in preterm infants. *Cochrane Database Syst Rev*. 2023;10:CD013830. doi: 10.1002/14651858.CD013830.pub2.

Section 5.2

Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. *World J Clin Pediatr*. 2015;4:81–93. doi: 10.5409/wjcp.v4.i4.81.